APPENDIX 5

Goodman & Gilman's The Pharmacological Basis of Therapeutics, Ninth Edition (1996), McGraw-Hill (p. 504, lines 6-10, left column)

Blaszczyk (1998) Acta Neurobiol Exp (Wars) 58:79-93 (see Abstract lines 12-14)

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CHAPTER 22

TREATMENT OF CENTRAL NERVOUS SYSTEM DEGENERATIVE DISORDERS

David G. Standaert and Anne B. Young

The neurodegenerative diseases include common and debilitating disorders such as Parkinson's disease, Alzheimer's disease, Huntington's disease, and amyotrophic lateral sclerosis (ALS). Although the clinical and neuropathological aspects of these disorders are distinct, their unifying feature is that each disorder has a characteristic pattern of neuronal degeneration in anatomically or functionally related regions.

Presently available pharmacological treatments for the neurodegenerative disorders are symptomatic and do not alter the course or progression of the underlying disease. The most effective symptomatic therapies are those for Parkinson's disease; a large number of agents from several different pharmacological classes can be used, and, when skillfully applied, these can have a dramatic impact on life span and functional ability. The treatments available for Alzheimer's disease, Huntington's disease, and ALS are less satisfactory but still can make an important contribution to patient welfare.

This chapter reviews current therapeutic agents for treatment of the symptoms of neurodegenerative diseases and introduces the reader to research aimed at developing therapeutic agents that alter the course of neurodegenerative diseases by preventing neuronal death or stimulating neuronal recovery. Related material concerning the serotonergic effects of some of the therapeutic agents employed for Parkinson's disease can be found in Chapter 11, and additional information concerning cholinergic agents that are used in treatment of Alzheimer's disease can be found in Chapters 7 and 8.

Neurodegenerative disorders are characterized by progressive and irreversible loss of neurons from specific regions of the brain. Prototypical neurodegenerative disorders include Parkinson's disease (PD) and Huntington's disease (HD), where loss of neurons from structures of the basal ganglia results in abnormalities in the control of movement; Alzheimer's disease (AD), where the loss of hippocampal and cortical neurons leads to impairment of memory and cognitive ability; and amyotrophic lateral sclerosis (ALS), where muscular weakness results from the degeneration of spinal, bulbar, and cortical motor neurons. As a group, these disorders are relatively common and represent a substantial medical and societal problem. They are primarily disorders of later life, developing in individuals who are neurologically normal, although childhood-onset forms of each of the disorders are recognized. PD is observed in more than 1% of individuals over the age of 65 (Tanner, 1992), whereas AD affects as much as 10% of the same population (Evans *et al.*, 1989). HD, which is a genetically determined autosomal dominant disorder, is less frequent in the population as a whole. ALS also is relatively rare, but often leads rapidly to disability and death (Kurtzke, 1982).

At present the pharmacological therapy of neurodegenerative disorders is limited to symptomatic treatments that do not alter the course of the underlying disease. Symptomatic treatment for PD, where the neurochemical deficit produced by the disease is well defined, is in general relatively successful, and a number of effective agents are available (Calne, 1993; Standaert and Stern, 1993). The available treatments for AD, HD, and ALS are much more limited in effectiveness, and the need for new strategies is particularly acute.

SELECTIVE VULNERABILITY AND NEUROPROTECTIVE STRATEGIES

Selective Vulnerability. The most striking feature of this group of disorders is the exquisite specificity of the disease processes for particular types of neurons. For example, in PD there is extensive destruction of the dopaminergic neurons of the substantia nigra, while neurons in the cortex and many other areas of the brain are unaffected (Gibb, 1992; Fearnley and Lees, 1994). In contrast, neural injury in AD is most severe in the hippocampus and neocortex, and even within the cortex, the loss of neurons is not uniform but varies dramatically in different functional regions (Arnold *et al.*, 1991). Even more striking is the observation that, in HD, the mutant gene responsible for the disorder is expressed throughout the brain and in many other organs, yet the pathological changes are largely restricted to the neostriatum (Vonsattel *et al.*, 1985; Landwehrmeyer *et al.*, 1994). In ALS, there is loss of spinal motor neurons and the cortical neurons that provide their descending input (Tandan and Bradley, 1985). The diversity of these patterns of neural degeneration has led to the proposal that the process of neural injury must be viewed as the interaction of genetic and environmental influences with the intrinsic physiological characteristics of the affected populations of neurons. These intrinsic factors may include susceptibility to excitotoxic injury, regional variation in capacity for oxidative metabolism, and the production of toxic free radicals as products of cellular metabolism (Figure 22–1). The factors that convey selective vulnerability may prove to be important targets for neuroprotective agents to slow the progression of neurodegenerative disorders.

Genetics and Environment. It long has been suspected that genetic predisposition plays an important role in the etiology of neurodegenerative disorders; this is certainly true for HD, which is transmitted by autosomal dominant inheritance. Families with a high incidence of PD, AD, or ALS also are well documented, yet manifestly familial cases constitute only a tiny fraction of the population of patients affected. A more subtle genetic influence, in the form of an inherited predisposition to neuronal injury that leads to the development of the disorder in response to particular environmental triggers, also may be active in these disorders (Golbe, 1990).

Infectious agents and environmental toxins also have been proposed as etiologic agents for neurodegenerative disorders. The role of infection is best documented in the numerous cases of PD that developed following the epidemic of encephalitis lethargica in the late 1910s; however, most contemporary cases of PD are not preceded by encephalitis, and there is no convincing evidence for an infectious contribution to the development of AD, HD, or ALS. At least one toxin, N-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP; *discussed below*), can induce a condition closely resembling PD, but evidence for the widespread occurrence of this or a similar toxin in the environment is lacking (Tanner and Langston, 1990).

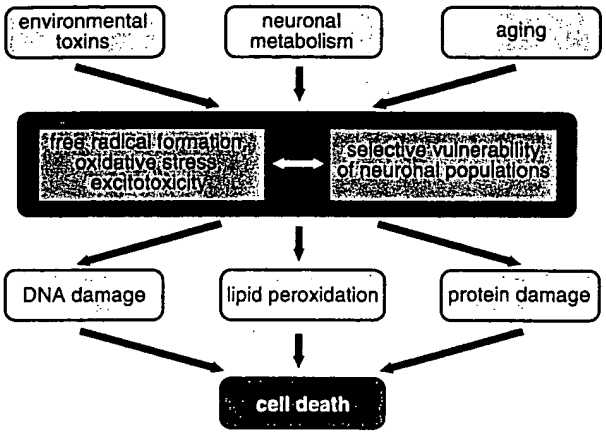

Figure 22–1. Mechanisms of selective neuronal vulnerability in neurodegenerative diseases.

Excitotoxicity. The term *excitotoxicity* was coined by Olney (1969) to describe the neural injury that results from the presence of excess glutamate in the brain. Glutamate is used as a neurotransmitter by many different neural systems and is believed to mediate most excitatory synaptic transmission in the mammalian brain. Although glutamate is required for normal brain function, the presence of excessive amounts of glutamate can lead to excitotoxic cell death (Lipton and Rosenberg, 1994). The destructive effects of glutamate are mediated by glutamate receptors, particularly those of the N-methyl-D-aspartate (NMDA) type. Unlike other glutamate-gated ion channels, which primarily regulate the flow of Na^+, activated NMDA receptor-channels allow an influx of Ca^{2+}, which in excess can activate a variety of potentially destructive processes. The activity of NMDA receptor-channels is regulated not only by the concentration of glutamate in the synaptic space, but also by a voltage-dependent blockade of the channel by Mg^{2+}; thus, entry of Ca^{2+} into neurons through NMDA receptor-channels requires binding of glutamate to NMDA receptors as well as depolarization of the neuron (*e.g.*, by the activity of glutamate at non-NMDA receptors), which relieves the blockade of NMDA channels by extracellular Mg^{2+}. Excitotoxic injury is thought to make an important

contribution to the neural death that occurs in acute processes such as stroke and head trauma (Choi and Rothman, 1990). In the chronic neurodegenerative disorders, the role of excitotoxicity is less certain, but it is thought that regional and cellular differences in susceptibility to excitotoxic injury, conveyed, for example, by differences in types of glutamate receptors, may contribute to selective vulnerability (Young, 1993).

Energy, Metabolism, and Aging. The excitotoxic hypothesis provides a link between selective patterns of neuronal injury, the effects of aging, and observations on the metabolic capacities of neurons (Beal *et al.*, 1993). Since the ability of Mg^{2+} to block the NMDA receptor-channel is dependent on the membrane potential, disturbances that impair the metabolic capacity of neurons will tend to relieve Mg^{2+} blockade and predispose to excitotoxic injury. The capacity of neurons for oxidative metabolism declines progressively with age, perhaps in part because of a progressive accumulation of mutations in the mitochondrial genome (Wallace, 1992). Patients with PD exhibit several defects in energy metabolism which are even greater than expected for their age, most notably a reduction in the function of Complex I of the mitochondrial electron transport chain (Schapira *et al.*, 1990). Additional evidence for the role of metabolic defects in the etiology of neural degeneration comes from the study of patients who inadvertently self-administered MPTP, a "designer drug" that resulted in symptoms of severe and irreversible parkinsonism (Ballard *et al.*, 1985). Subsequent studies have shown that a metabolite of MPTP induces degeneration of neurons similar to that observed in idiopathic PD and that its mechanism of action appears to be related to an ability to impair mitochondrial energy metabolism in dopaminergic neurons (Tipton and Singer, 1993). In rodents, neural degeneration similar to that observed in HD can be produced either by direct administration of large doses of NMDA receptor agonists or by more chronic administration of inhibitors of mitochondrial oxidative metabolism, suggesting that disturbances of energy metabolism may underlie the selective pathology of HD as well (Beal *et al.*, 1986; Beal *et al.*, 1993).

Oxidative Stress. Although neurons depend on oxidative metabolism for survival, a consequence of this process is the production of reactive compounds such as hydrogen peroxide and oxyradicals (Cohen and Werner, 1994). Unchecked, these reactive species can lead to DNA damage, peroxidation of membrane lipids, and neuronal death. Several mechanisms serve to limit this *oxidative stress*, including the presence of reducing compounds such as ascorbate and glutathione and enzymatic mechanisms such as superoxide dismutase, which catalyzes the reduction of superoxide radicals. Oxidative stress also may be relieved by aminosteroid agents that serve as free radical scavengers (*see* Chapter 59). Recent genetic evidence has linked disturbances in the metabolism of oxyradicals by superoxide dismutase to the etiology of ALS (reviewed below). In PD, attention has been focused on the possibility that oxidative stress induced by the metabolism of dopamine may underlie the selective vulnerability of dopaminergic neurons observed in PD (Fahn and Cohen, 1992). The primary catabolic pathway of dopamine to 3,4-dihydroxyphenylacetic acid (DOPAC) is catalyzed by monoamine oxidase (MAO) and generates hydrogen peroxide. Hydrogen peroxide, in the presence of ferrous ion, which is relatively abundant in the basal ganglia, may generate hydroxyl free radicals (the Fenton reaction, Figure 22–2; Olanow, 1990). If the protective mechanisms are inadequate because of inherited or acquired deficiency, the oxyradicals could cause degeneration of dopaminergic neurons. Supporting this proposal is the observation of increased lipid hydroperoxides in the substantia nigra in PD (Jenner, 1991). This hypothesis has led to several proposals for therapeutic agents to retard neuronal loss in PD. Two candidates, the free radical scavenger *tocopherol* (vitamin E) and the MAO inhibitor *selegiline* (discussed *below*), have been tested in a large-scale clinical trial, but neither was shown to have a substantial neuroprotective effect (Parkinson's Study Group, 1993).

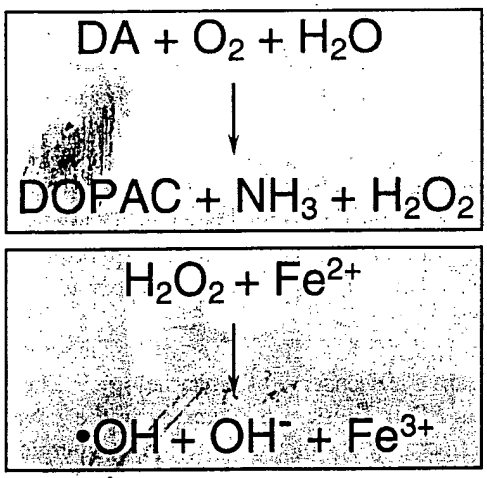

Figure 22–2. Production of free radicals by the metabolism of dopamine (DA).

DA is converted by monamine oxidase (MAO) and aldehyde dehydrogenase to 3,4-dihydroxyphenylacetic acid (DOPAC), producing hydrogen peroxide (H_2O_2). In the presence of ferrous iron, H_2O_2 undergoes spontaneous conversion, forming a hydroxyl free radical (the Fenton reaction).

PARKINSON'S DISEASE

Clinical Overview. Parkinsonism is a clinical syndrome comprising four cardinal features: bradykinesia (slowness and poverty of movement), muscular rigidity, resting tremor (which usually abates during voluntary movement), and an impairment of postural balance leading to disturbances of gait and falling. The most common cause of parkinsonism is idiopathic PD, first described by James Parkinson in 1817 as *paralysis agitans,* or the "shaking palsy." The pathological hallmark of PD is a loss of the pigmented, dopaminergic neurons of the substantia nigra pars compacta, with the appearance of intracellular inclusions known as Lewy bodies (Gibb, 1992; Fearnley and Lees, 1994). Progressive loss of dopamine neurons is a feature of normal aging; however, most people do not lose the 80% to 90% of dopaminergic neurons required to cause symptomatic PD. Without treatment, PD progresses over 5 to 10 years to a rigid, akinetic state in which patients are incapable of caring for themselves. Death frequently results from complications of immobility, including aspiration pneumonia or pulmonary embolism. The availability of effective pharmacological treatment has altered radically the prognosis of PD; in most cases, good functional mobility can be maintained for many years, and the life expectancy of adequately treated patients is substantially increased (Diamond *et al.,* 1987). It is important to recognize that several disorders other than PD also may produce parkinsonism, including some relatively rare neurodegenerative disorders, stroke, and intoxication with dopamine receptor-blocking drugs. Drugs in common clinical use that may cause parkinsonism include antipsychotics such as haloperidol and thorazine (*see* Chapter 18) and antiemetics such as prochlorperazine and metoclopramide (*see* Chapter 38). Although a complete discussion of the clinical diagnostic approach to parkinsonism exceeds the scope of this chapter, the distinction between PD and other causes of parkinsonism is important, because parkinsonism arising from other causes is usually refractory to all forms of treatment.

Parkinson's Disease: Pathophysiology. The primary deficit in PD is a loss of the neurons in the substantia nigra pars compacta which provide dopaminergic innervation to the striatum (caudate and putamen). The current understanding of the pathophysiology of PD can be traced to the classical neurochemical investigations in the 1950s and 1960s, in which a more than 80% reduction in the striatal dopamine content was demonstrated. This parallelled the loss of neurons from the substantia nigra, suggesting that replacement of dopamine could restore function (Cotzias *et al.,* 1969; Hornykiewicz, 1973). These fundamental observations led to an extensive investigative effort to understand the metabolism and actions of dopamine and to learn how a deficit in dopamine gives rise to the clinical features of PD. This effort led to a current model of the function of the basal ganglia that admittedly is incomplete but is still useful.

Biosynthesis of Dopamine. Dopamine, a catecholamine, is synthesized in the terminals of dopaminergic neurons from tyrosine, which is transported across the blood–brain barrier by an active process (Figures 22–3 and 22–4). The rate-limiting step in the synthesis of dopamine is the conversion of L-tyrosine to L-dihydroxyphenylalanine (L-DOPA), catalyzed by the enzyme tyrosine hydroxylase which is present within catecholaminergic neurons.

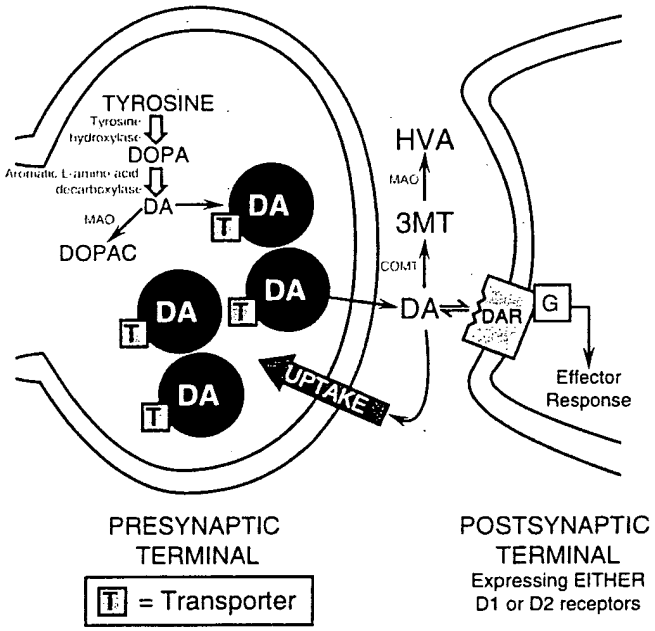

Figure 22–3. Dopaminergic terminal.

Dopamine (DA) is synthesized within neuronal terminals from the precursor tyrosine by the sequential actions of the enzymes tyrosine hydroxylase, producing the intermediary L-dihydroxyphenylalanine (DOPA), and aromatic L-amino acid decarboxylase. In the terminal, dopamine is transported into storage vesicles by a transporter protein (T) associated with the vesicular membrane. Release, triggered by depolarization and entry of Ca^{2+}, allows dopamine to act on postsynaptic dopamine receptors (DAR); as discussed in the text, several distinct types of dopamine receptors are present in the brain, and the differential actions of dopamine on postsynaptic targets bearing different types of dopamine receptors have important implications for the function of neural circuits. The actions of dopamine are terminated by the sequential actions of the enzymes catechol-O-methyl-transferase (COMT) and monoamine oxidase (MAO), or by reuptake of dopamine into the terminal.

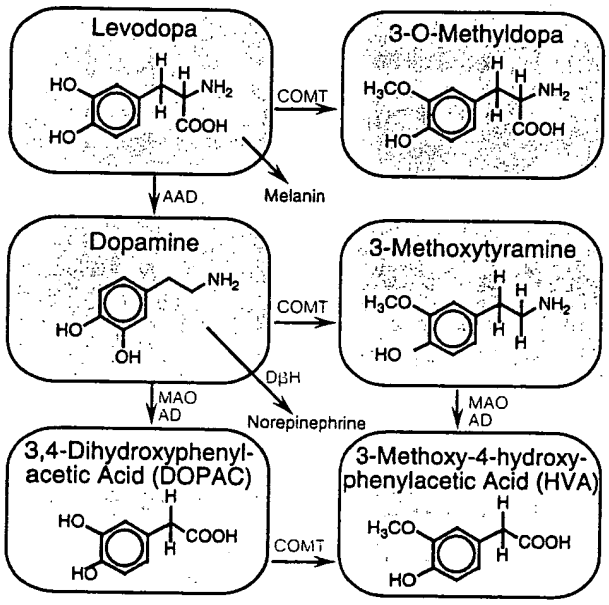

Figure 22–4. Metabolism of levodopa (L-DOPA).

AD, aldehyde dehydrogenase; COMT, catechol-O-methyl transferase; DβH, dopamine β-hydroxylase; AAD, aromatic L-amino acid decarboxylase; MAO, monoamine oxidase.

L-DOPA is converted rapidly to dopamine by aromatic L-amino acid decarboxylase. In dopaminergic nerve terminals, dopamine is taken up into vesicles by a transporter protein; this process is blocked by reserpine, which leads to depletion of dopamine. Release of dopamine from nerve terminals occurs through exocytosis of presynaptic vesicles, a process that is triggered by depolarization leading to entry of Ca^{2+}. Once dopamine is in the synaptic cleft, its actions may be terminated by reuptake through a membrane carrier protein, a process antagonized by drugs such as cocaine. Alternatively, dopamine can be degraded by the sequential actions of monoamine oxidase (MAO) and catechol-O-methyl transferase (COMT) to yield two metabolic products, 3,4-dihydroxyphenylacetic acid (DOPAC) and 3-methoxy-4-hydroxyphenylacetic acid (HVA; *see* Chapter 12). In human beings, HVA is the primary product of the metabolism of dopamine (Cooper *et al.*, 1991).

Dopamine Receptors. The actions of dopamine in the brain are mediated by a family of dopamine receptor proteins (Figure 22–5). Two types of dopamine receptors were identified in the mammalian brain using pharmacological techniques: D1 receptors, which stimulate the synthesis of the intracellular second messenger cyclic AMP, and D2 receptors, which inhibit cyclic AMP synthesis. The recent application of molecular genetics to the study of dopamine receptors has provided a wealth of information regarding the structures of these proteins and has revealed a more complex receptor situation than originally envisioned. At present, five distinct dopamine receptors are known to exist (*see* Jarvie and Caron, 1993, and Chapter 12). The dopamine receptors share several structural features, including the presence of seven α-helical segments capable of spanning the cell membrane. This structure identifies the dopamine receptors as members of the larger superfamily of seven-transmembrane-region receptor proteins, which includes other important neural receptors such as β-adrenergic receptors, olfactory receptors, and the visual pigment rhodopsin. All members of this superfamily act through guanine nucleotide-binding proteins (G proteins; *see* Chapter 2).

The five dopamine receptors can be divided into two groups on the basis of their pharmacological and structural properties (Figure 22–5). The D1 and D5 proteins have a long intracellular carboxy-terminal tail and are members of the pharmacologically defined D1 class; they stimulate the formation of cyclic AMP and phosphatidyl

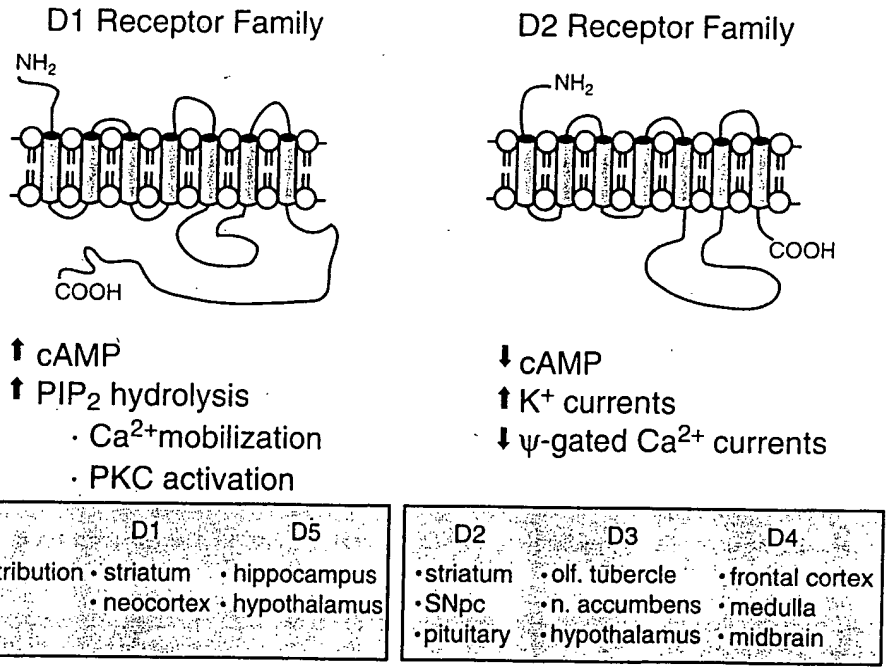

Figure 22–5. Distribution and characteristics of dopamine receptors.

SNpc, substantia nigra pars compacta; cAMP, cyclic AMP; Ψ, voltage.

inositol hydrolysis. The D2, D3, and D4 receptors share a large third intracellular loop and are of the D2 class. They decrease cyclic AMP formation and modulate K^+ and Ca^{2+} currents. Each of the five dopamine receptor proteins has a distinct anatomical pattern of expression in the brain. The D1 and D2 proteins are abundant in the striatum and are the most important receptor sites with regard to the causes and treatment of PD. The D4 and D5 proteins are largely extrastriatal, while D3 expression is low in the caudate and putamen but more abundant in the nucleus accumbens and olfactory tubercle.

Neural Mechanism of Parkinsonism. Considerable effort has been devoted in recent years to understanding how the loss of dopaminergic input to the neurons of the neostriatum gives rise to the clinical features of PD (for review *see* Albin *et al.*, 1989; Mink and Thach, 1993; and Wichmann and DeLong, 1993). The basal ganglia can be viewed as a modulatory side loop that regulates the flow of information from the cerebral cortex to the motor neurons of the spinal cord (Figure 22–6). The neostriatum is the principal input structure of the basal ganglia and receives excitatory glutamatergic input from many areas of the cortex. The majority of neurons within the striatum are projection neurons that innervate other basal ganglia structures. A small but important subgroup of striatal neurons are interneurons that interconnect neurons within the striatum but do not project beyond its borders. Acetylcholine as well as neuropeptides are used as transmitters by the striatal interneurons. The outflow of the striatum proceeds along two distinct routes, identified as the direct and indirect pathways. The direct pathway is formed by neurons in the striatum that project directly to the output stages of the basal ganglia, the substantia nigra pars reticulata (SNpr) and the medial globus pallidus (MGP); these in turn relay to the ventroanterior and ventrolateral thalamus, which provides excitatory input to the cortex. The neurotransmitter of both links of the direct pathway is gamma-aminobutyric acid (GABA), which is inhibitory, so that the net effect of stimulation of the direct pathway at the level of the striatum is to increase the excitatory outflow from the thalamus to the cortex. The indirect pathway is composed of striatal neurons that project to the lateral globus pallidus (LGP). This structure in turn innervates the subthalamic nucleus (STN), which provides outflow to the SNpr and MGP output stage. As in the direct pathway, the first two links, the projections from striatum to LGP and LGP to STN, use the inhibitory transmitter GABA; however, the final link, the projection from STN to SNpr and MGP, is an excitatory glutamatergic pathway. Thus the net effect of stimulating the indirect pathway at the level of the striatum is to reduce the excitatory outflow from the thalamus to the cerebral cortex.

The key feature of this model of basal ganglia function, which accounts for the symptoms observed in PD as a result of loss of dopaminergic neurons, is the differential effect of dopamine on the direct and indirect pathways (Figure 22–7). The dopaminergic neurons of the substantia nigra pars compacta (SNpc) innervate all parts of the striatum; however, the target striatal neurons express distinct types of dopamine receptors. The striatal neurons giving rise to the direct pathway express primarily the *excitatory* D1 dopamine receptor protein, while the striatal neurons forming the indirect pathway express primarily the *inhibitory* D2 type. Thus, dopamine released in the striatum tends to increase the activity of the direct pathway and reduce the activity of the indirect pathway, whereas the depletion that occurs in PD has the opposite effect. The net effect of the reduced dopaminergic input in PD is to markedly increase the inhibitory outflow from the SNpr and MGP to the thalamus and reduce excitation of the motor cortex.

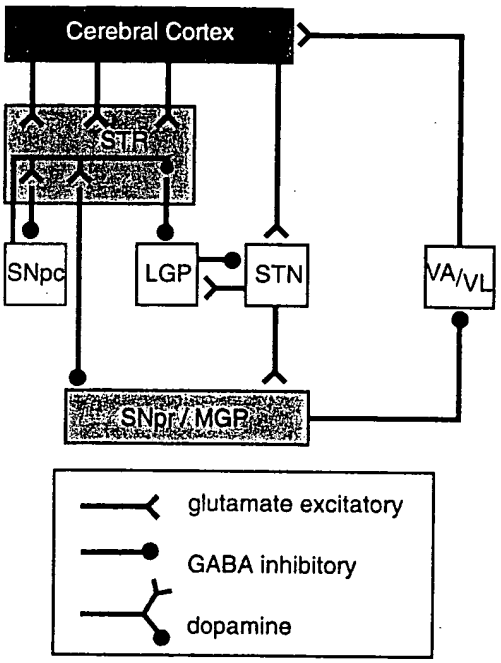

Figure 22–6. Schematic wiring diagram of the basal ganglia.

The neostriatum (STR) is the principal input structure of the basal ganglia and receives excitatory, glutamatergic input from many areas of cerebral cortex. Outflow from the STR proceeds along two routes. The direct pathway, from the STR to the substantia nigra pars reticulata (SNpr) and medial globus pallidus (MGP), uses the inhibitory tramsmitter GABA. The indirect pathway, from the STR through the lateral globus pallidus (LGP) and the subthalamic nucleus (STN) to the SNpr and MGP consists of two inhibitory, GABAergic links and one excitatory, glutamatergic projection. The substantia nigra pars compacta (SNpc) provides dopaminergic innervation to the striatal neurons giving rise to both the direct and indirect pathways, and regulates the relative activity of these two paths. The SNpr and MGP are the output structures of the basal ganglia, and provide feedback to the cerebral cortex through the ventroanterior and ventrolateral nuclei of the thalamus (VA/VL).

This model of basal ganglia function has important implications for the rational design and use of pharmacological agents in PD. First, it suggests that to restore the balance of the system through stimulation of dopamine receptors, the complementary effect of actions at both D1 and D2 receptors, as well as the possibility of adverse effects which may be mediated by D3, D4, or D5 receptors, must be considered. Second, it explains why replacement of dopamine is not the only approach to the treatment of PD. Drugs that inhibit cholinergic receptors long have been used for treatment of parkinsonism. Although their mechanisms of action are not completely understood, it seems likely that their effect is mediated at the level of the striatal projection neurons which normally receive cholinergic input from

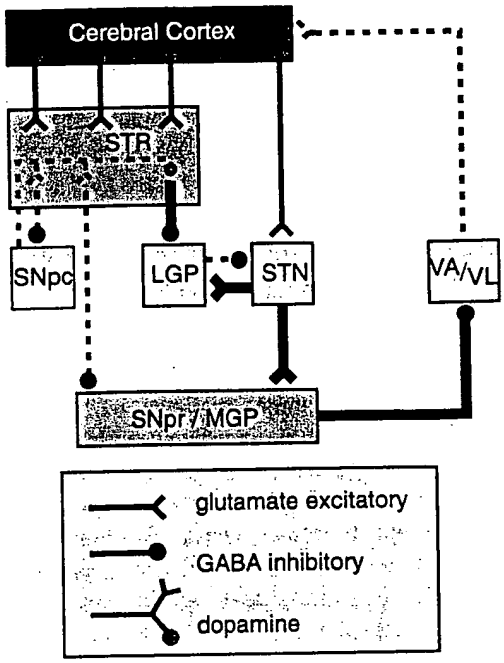

Figure 22–7. The basal ganglia in Parkinson's disease (PD).

The primary defect is destruction of the dopaminergic neurons of the SNpc. The striatal neurons which form the direct pathway from the STR to the SNpr and MGP express primarily the *excitatory* D1 dopamine receptor, while the striatal neurons which project to the LGP and form the indirect pathway express the *inhibitory* D2 dopamine receptor. Thus, loss of the dopaminergic input to the striatum has a differential effect on the two outflow pathways; the direct pathway to the SNpr and MGP is less active, while the activity in the indirect pathway is increased. The net effect is that neurons in the SNpr and MGP become more active. This leads to increased inhibition of the VA/VL thalamus and reduced excitatory input to the cortex. Thin line, normal pathway activity; thick line, increased pathway activity in PD; dashed line, reduced pathway activity in PD. (*See* legend to Figure 22–6 for definitions of anatomical abbreviations.)

striatal cholinergic interneurons. No clinically useful drugs for parkinsonism are presently available based on actions through GABA and glutamate receptors, even though both have crucial roles in the circuitry of the basal ganglia. However, they represent a promising avenue for drug development (Greenamyre and O'Brien, 1991).

Treatment of Parkinson's Disease

Commonly used medications for the treatment of PD are summarized in Table 22–1.

Levodopa. *Levodopa* (L-DOPA, LARODOPA, DOPAR, L-3,4-dihydroxyphenylalanine), the metabolic precursor of dopamine, is the single most effective agent in the treatment of PD. Levodopa is itself largely inert; its therapeutic as well as adverse effects result from the decarboxylation of levodopa to dopamine. When administered orally, levodopa is rapidly absorbed from the small bowel by an active transport system for aromatic amino acids. Concentrations of the drug in plasma usually peak between 0.5 and 2 hours after an oral dose. The half-life in plasma is

Table 22–1
Drugs for Parkinson's Disease

AGENT	TYPICAL INITIAL DOSE	DAILY DOSE— USEFUL RANGE	COMMENTS
Carbidopa/levodopa	25 to 100 mg twice a day or three times a day	200 to 1200 mg levodopa	
Carbidopa/levodopa sustained release	50 to 200 mg twice a day	200 to 1200 mg levodopa	Bioavailability 75% of standard form
Pergolide	0.05 mg once a day	0.75 to 5.0 mg	Titrate slowly
Bromocriptine	1.25 mg twice a day	3.75 to 40 mg	Titrate slowly
Selegiline	5.0 mg twice a day	2.5 to 10 mg	
Amantadine	100 mg twice a day	200 mg	
Trihexyphenidyl HCl	1 mg twice a day	2 to 15 mg	

short (1 to 3 hours). The rate and extent of absorption of levodopa is dependent upon the rate of gastric emptying, the pH of gastric juice, and the length of time the drug is exposed to the degradative enzymes of the gastric and intestinal mucosa. Competition for absorption sites in the small bowel from dietary amino acids also may have a marked effect on the absorption of levodopa; administration of levodopa with meals delays absorption and reduces peak plasma concentrations. Entry of the drug into the central nervous system (CNS) across the blood–brain barrier also is an active process mediated by a carrier of aromatic amino acids, and competition between dietary protein and levodopa may occur at this level. In the brain, levodopa is converted to dopamine by decarboxylation, primarily within the presynaptic terminals of dopaminergic neurons in the striatum. The dopamine produced is responsible for the therapeutic effectiveness of the drug in PD; after release, it is either transported back into dopaminergic terminals by the presynaptic uptake mechanism or metabolized by the actions of MAO and COMT (Mouradian and Chase, 1994).

In modern practice, levodopa is almost always administered in combination with a peripherally acting inhibitor of aromatic L-amino acid decarboxylase, such as *carbidopa* or *benserazide*. If levodopa is administered alone, the drug is largely decarboxylated by enzymes in the intestinal mucosa and other peripheral sites that are rich in MAO, so that relatively little unchanged drug reaches the cerebral circulation and probably less than 1% penetrates the CNS. In addition, dopamine released into the circulation by peripheral conversion of levodopa produces undesirable effects, particularly nausea. Inhibition of peripheral decarboxylase markedly increases the fraction of administered levodopa that remains unmetabolized and available to cross the blood–brain barrier and reduces the incidence of gastrointestinal side effects. In most individuals, a daily dose of 75 mg of carbidopa is sufficient to prevent the development of nausea. For this reason, the most commonly prescribed form of carbidopa/levodopa (SINEMET, ATAMET) is the *25/100* form, containing 25 mg of carbidopa and 100 mg of levodopa. With this formulation, dosage schedules of three or more tablets daily provide acceptable inhibition of decarboxylase in most individuals. Occasionally, individuals will require larger doses of carbidopa to minimize gastrointestinal side effects, and administration of supplemental carbidopa alone may be beneficial.

Levodopa therapy can have a dramatic effect on all the signs and symptoms of PD. Early in the course of the disease, the degree of improvement in tremor, rigidity, and bradykinesia may be nearly complete. In early PD, the duration of the beneficial effects of levodopa may exceed the plasma lifetime of the drug, suggesting that the nigrostriatal dopamine system retains some capacity to store and release dopamine. A principal limitation of the long-term use of levodopa therapy is that, with time, this apparent "buffering" capacity is lost, and the patient's motor state may fluctuate dramatically with each dose of levodopa. A common problem is the development of the "wearing off" phenomenon; each dose of levodopa effectively improves mobility for a period of time, perhaps 1 to 2 hours, but rigidity and akinesia rapidly return at the end of the dosing interval. Increasing the dose and frequency of administration can improve this situation, but this is often limited by development of dyskinesias, excessive and abnormal involuntary movements. Dyskinesias are most often observed when the plasma levodopa concentration is high, although in some individuals dyskinesias or dystonia may be triggered when the level is rising or falling. These movements can be as uncomfortable and disabling as the rigidity and akinesia of PD. In the later stages of PD, patients may fluctuate rapidly between being "off," having no beneficial effects from their medications, and being "on" but with disabling dyskinesias, a situation called the "on/off phenomenon."

Recent evidence has indicated that the induction of on/off phenomena and dyskinesias may be the result of an active process of adaptation to variations in brain and plasma levodopa levels. This process of adaptation is apparently complex, involving not only alterations in the expression of dopamine receptor proteins but also downstream changes in the postsynaptic striatal neurons (Mouradian and Chase, 1994). When levodopa levels are maintained at a constant level by intravenous infusion, dyskinesias and fluctuations are greatly reduced, and the clinical improvement is maintained for up to several days after returning to oral levodopa dosing (Mouradian *et al.*, 1990; Chase *et al.*, 1994). A sustained-release formulation consisting of carbidopa/levodopa in an erodable wax matrix (SINEMET CR) has been marketed in an attempt to produce more stable plasma levodopa levels than can be obtained with oral administration of standard carbidopa/levodopa formulations. This formulation is helpful in some cases, but the absorption of the sustained release formulation is not entirely predictable. Another technique used to overcome the on/off phenomenon is to sum the total daily dose of carbidopa/levodopa and give equal amounts every 2 hours rather than every 4 or 6 hours.

An important unanswered question regarding the use of levodopa in PD is whether this medication alters the course of the underlying disease or merely modifies the symptoms. Two aspects of levodopa treatment and the outcome of PD are of concern. First, it has been suggested that if the production of free radicals as a result of dopamine metabolism contributes to the death of nigrostriatal neurons, the addition of levodopa might actually accelerate the process (Olanow, 1990), although no convincing evidence for such an effect has yet been obtained. Second, it is well established that the undesirable on/off fluctuations and wearing off phenomena are observed almost exclusively in patients treated with levodopa, but it is not

known if delaying treatment with levodopa will delay the appearance of these effects. In view of these uncertainties, most practitioners have adopted a pragmatic approach, using levodopa only when the symptoms of PD cause functional impairment.

In addition to motor fluctuations and nausea, several other adverse effects may be observed with levodopa treatment. A common and troubling adverse effect is the induction of hallucinations and confusion; these effects are particularly common in the elderly and in those with pre-existing cognitive dysfunction and often limit the ability to treat parkinsonian symptoms adequately. Conventional antipsychotic agents, such as the phenothiazines, are effective against levodopa-induced psychosis but may cause marked worsening of parkinsonism, probably through actions at the D2 dopamine receptor. A recent approach has been to use the atypical neuroleptic clozapine, which is effective in the treatment of psychosis but does not cause or worsen parkinsonism (Greene *et al.*, 1993). The mechanism of action of clozapine is not understood; it may have actions at receptors for dopamine, acetylcholine, and serotonin (*see* Chapters 11 and 12).

Peripheral decarboxylation of levodopa and release of dopamine into the circulation may activate vascular dopamine receptors and produce orthostatic hypotension. The actions of dopamine at α and β adrenergic receptors may induce cardiac arrhythmias, especially in patients with pre-existing conduction disturbances. Administration of levodopa with nonspecific inhibitors of MAO, such as *pargyline*, markedly accentuates the actions of levodopa and may precipitate life-threatening hypertensive crisis and hyperpyrexia; nonspecific MAO inhibitors should always be discontinued at least 14 days before levodopa is administered (note that this prohibition does not include the MAO-B subtype-specific inhibitor selegiline, which, as discussed below, often is administered safely in combination with levodopa). Abrupt withdrawal of levodopa or other dopaminergic medications may precipitate the *neuroleptic malignant syndrome* more commonly observed after treatment with dopamine antagonists (Keyser and Rodnitzky, 1991).

Dopamine Receptor Agonists. An alternative to levodopa is the use of drugs that are direct agonists of striatal dopamine receptors, an approach which offers several potential advantages. Since enzymatic conversion of these drugs is not required for activity, they do not depend on the functional capacities of the nigrostriatal neurons and thus might be more effective than levodopa in late PD. In addition, dopamine agonists potentially are more selective in their actions; unlike levodopa, which leads to activation of all dopamine receptor types throughout the brain, agonists may exhibit relative selectivity for different subtypes of dopamine receptors. Most of the dopamine agonists in current clinical use have durations of action substantially longer than that of levodopa and are often useful in the management of dose-related fluctuations in motor state. Finally, if the hypothesis that free radical formation as a result of dopamine metabolism contributes to neuronal death is correct, then dopamine agonists have the potential to modify the course of the disease by reducing endogenous release of dopamine as well as the need for exogenous levodopa (Goetz, 1990).

Two dopamine agonists, *bromocriptine* (PARLODEL) and *pergolide* (PERMAX), currently are available in the United States for treatment of PD (Figure 22–8). Both are ergot derivatives, and although their *in vitro* pharmacological properties are somewhat different, their actions and spectrum of adverse effects are similar. Bromocriptine is a strong agonist of the D2 class of dopamine receptors and a partial antagonist of the D1 class of receptors, while pergolide acts as an agonist at both D1 and D2 receptor subtypes. Both are well absorbed orally and have plasma half-lives in the range of 3 to 7 hours. Pergolide is substantially more potent than bromocriptine; typical, therapeutic doses of pergolide are 0.75 to 3 mg per day (maximum recommended dose is 5 mg per day), while daily doses of bromocriptine are 2.5 mg to as high as 40 mg. The actions and adverse effects of these drugs are similar to those of levodopa. Both bromocriptine and pergolide are effective in relieving the clinical symptoms of PD. Their duration of action after a single dose often is longer than that of levodopa, and thus a lessening of on/off fluctuations can be observed, although both drugs can cause dyskinesias. Like levodopa, these drugs may cause orthostatic hypotension. Rarely, profound hypotension may be observed after the initial dose of bromocriptine or pergolide; for this reason, these drugs should be initiated at low dosage, and the administered dose should be adjusted upward slowly, particularly in patients who are taking other antihypertensive medications or have pre-existing orthostatic hypotension. Both bromocriptine and pergolide may induce hallucinosis or confusion similar to that observed with levodopa; this effect often limits the dose of these drugs that may be used. In addition to effects related to their actions at dopamine receptors, bromocriptine and pergolide share some properties with the parent family of ergot compounds, including the ability to induce pleuropulmonary and retroperitoneal fibrosis, erythromyalgia, and digital vasospasm.

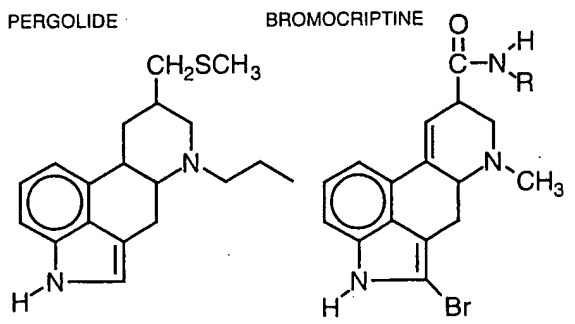

Figure 22–8. Structures of direct agonists of dopamine receptors.

In current practice, the most common use of dopamine agonists in the treatment of PD is in combination with carbidopa/levodopa in patients with fairly advanced PD who are experiencing dose-related fluctuation in their motor state. Use of dopamine agonist monotherapy as initial treatment of PD has been advocated, based in part on the theoretical reduction in oxidative stress resulting from reduced turnover of dopamine. At present there are no substantial data to support a neuroprotective effect of dopamine agonists, and many practitioners have found that the clinical efficacy of dopamine agonist monotherapy is less satisfactory than that of levodopa (Factor and Weiner, 1993). Several drugs that are more specific agonists of particular dopamine receptor subtypes are in development and may eventually prove to be very useful.

Selegiline. Two isoenzymes of MAO oxidize monoamines. While both isoenzymes (MAO-A and MAO-B) are present in the periphery and inactivate monoamines of intestinal origin, the isoenzyme MAO-B is the predominant form in the striatum and is responsible for the majority of oxidative metabolism of dopamine in the striatum. At low-to-moderate doses (10 mg/day or less), *selegiline* (ELDEPRYL) is a selective inhibitor of MAO-B, leading to irreversible inhibition of the enzyme (Olanow, 1993). Unlike nonspecific inhibitors of MAO (such as phenelzine and isocarboxazid), selegiline does not inhibit peripheral metabolism of catecholamines; thus, it can be taken safely with levodopa, and it does not cause the lethal potentiation of catecholamine action observed when patients taking nonspecific MAO inhibitors ingest indirectly acting sympathomimetic amines such as the tyramine found in certain cheeses and wine. Doses of selegiline higher than 10 mg daily can produce inhibition of MAO-A and should be avoided.

Selegiline has been used for several years as a symptomatic treatment for PD, although its benefit is fairly modest. The basis of the efficacy of selegiline is presumed to be its ability to retard the breakdown of dopamine in the striatum. With the recent emergence of interest in the potential role of free radicals and oxidative stress in the pathogenesis of PD, it has been proposed that the ability of selegiline to retard the metabolism of dopamine might confer neuroprotective properties. In support of this idea, it was observed that selegiline could protect animals from MPTP-induced parkinsonism by blocking the conversion of MPTP to its toxic metabolite (1-methyl-4-phenylpyridium ion), a transformation mediated by MAO-B. The potential protective role of selegiline in idiopathic PD was evaluated recently in multicenter randomized trials; these studies showed a symptomatic effect of selegiline in PD, but longer follow-up failed to provide any definite evidence of ability to retard the loss of dopaminergic neurons (Parkinson's Study Group, 1993).

Selegiline is generally well tolerated in patients with early or mild PD. In patients with more advanced PD or underlying cognitive impairment, selegiline may accentuate the adverse motor and cognitive effects of levodopa therapy. Metabolites of selegiline include amphetamine and methamphetamine, which may cause anxiety, insomnia, and other adverse symptoms. Interestingly, it has been observed that selegiline, like the nonspecific MAO inhibitors, can lead to the development of stupor, rigidity, agitation, and hyperthermia after administration of the analgesic meperidine; the basis of this interaction is uncertain.

Muscarinic Receptor Antagonists. Antagonists of muscarinic acetylcholine receptors were widely used for the treatment of PD before the discovery of levodopa. The biological basis for the therapeutic actions of anticholinergics is not completely understood. It seems likely that they act within the neostriatum, through the receptors that normally mediate the response to the intrinsic cholinergic innervation of this structure, which arises primarily from cholinergic striatal interneurons. Several muscarinic cholinergic receptors have been cloned (*see* Chapters 7 and 12); like the dopamine receptors, these are proteins with seven transmembrane domains that are linked to second-messenger systems by G proteins. Five subtypes of muscarinic receptor have been identified; at least four and probably all five subtypes are present in the striatum, although each has a distinct distribution (Hersch *et al.*, 1994). Several drugs with anticholinergic properties are currently used in the treatment of PD, including *trihexyphenidyl* (ARTANE, 2 to 4 mg, three times per day), *benzotropine mesylate* (COGENTIN, 1 to 4 mg, two times per day), and *diphenhydramine hydrochloride* (BENEDRYL, 25 to 50 mg, 3 to 4 times per day). All have a modest antiparkinsonian action, which is useful in the treatment of early PD or as an adjunct to dopamimetic therapy. The adverse effects of these drugs are a result of their anticholinergic properties. Most troublesome is sedation and mental confusion, frequently seen in the elderly. They also may produce constipation, urinary retention, and blurred vision through cycloplegia; they must be used with caution in narrow-angle glaucoma.

Amantadine. *Amantadine,* an antiviral agent used for the prophylaxis and treatment of influenza A (*see* Chapter 50), has antiparkinsonian actions. The mechanism of action of amantadine is not clear. It has been suggested that it might alter dopamine release or reuptake; anticholinergic properties also may contribute to its therapeutic actions. Amantadine and the closely related compound memantadine recently were shown to have activity at glutamate receptors, which may contribute to their antiparkinsonian actions (Stoof *et al.*, 1992). In any case, the effects of amantadine in PD are modest. It is used as initial therapy of mild PD. It may also be helpful as an adjunct in patients on levodopa with dose-related fluctuations. Amantadine usually is ad-

ministered in a dose of 100 mg twice a day and is well tolerated. Dizziness, lethargy, and sleep disturbance, as well as nausea and vomiting, have been observed occasionally, but even when present these effects are mild and reversible.

ALZHEIMER'S DISEASE

Clinical Overview. AD produces an impairment of cognitive abilities that is gradual in onset but relentless in progression. Impairment of short-term memory is usually the first clinical feature, while retrieval of distant memories is preserved relatively well into the course of the disease. As the condition progresses, additional cognitive abilities are impaired, among them the ability to calculate, visuospatial skills, and the ability to use common objects and tools (ideomotor apraxia). The level of arousal or alertness of the patient is not affected until the condition is very advanced, nor is there motor weakness, although muscular contractures are an almost universal feature of advanced stages of the disease. Death, most often from a complication of immobility such as pneumonia or pulmonary embolism, usually ensues within 6 to 12 years after onset. The diagnosis of AD is based on careful clinical assessment of the patient and appropriate laboratory tests to exclude other disorders that may mimic AD; at present, no direct antemortem confirmatory test exists.

Pathophysiology. AD is characterized by marked atrophy of the cerebral cortex and loss of cortical and subcortical neurons. The pathological hallmarks of AD are senile plaques, which are spherical accumulations of the protein β-amyloid accompanied by degenerating neuronal processes, and neurofibrillary tangles, composed of paired helical filaments and other proteins (Arnold *et al.*, 1991; Arriagada *et al.*, 1992; Braak and Braak, 1994). Although small numbers of senile plaques and neurofibrillary tangles can be observed in intellectually normal individuals, they are far more abundant in AD, and the abundance of tangles is roughly proportional to the severity of cognitive impairment. In advanced AD, senile plaques and neurofibrillary tangles are numerous. They are most abundant in the hippocampus and associative regions of the cortex, whereas areas such as the visual and motor cortices are relatively spared. This corresponds to the clinical features of marked impairment of memory and abstract reasoning with preservation of vision and movement. The factors underlying the selective vulnerability of particular cortical neurons to the pathological effects of AD are not known.

Neurochemistry. The neurochemical disturbances that arise in AD have been studied intensively (Johnston, 1992). Direct analysis of neurotransmitter content in the cerebral cortex shows a reduction of many transmitter substances that parallels neuronal loss; there is a striking and disproportionate deficiency of acetylcholine. The anatomical basis of the cholinergic deficit is the atrophy and degeneration of subcortical cholinergic neurons, particularly those in the basal forebrain (nucleus basalis of Meynert), that provide cholinergic innervation to the whole cerebral cortex. The selective deficiency of acetylcholine in AD, as well as the observation that central cholinergic antagonists such as atropine can induce a confusional state that bears some resemblance to the dementia of AD, has given rise to the "cholinergic hypothesis," which proposes that a deficiency of acetylcholine is critical in the genesis of the symptoms of AD (Perry, 1986). Although the conceptualization of AD as a "cholinergic deficiency syndrome" in parallel with the "dopaminergic deficiency syndrome" of PD provides a useful framework, it is important to note that the deficit in AD is far more complex, involving multiple neurotransmitter systems, including serotonin, glutamate, and neuropeptides, and that in AD there is destruction of not only cholinergic neurons but also the cortical and hippocampal targets that receive cholinergic input.

Role of β-amyloid. The presence of aggregates of β-amyloid is a constant feature of AD. Until recently, it was not clear whether the amyloid protein was causally linked to the disease process or merely a by-product of neuronal death. The application of molecular genetics has shed considerable light on this question. β-Amyloid was isolated from affected brains and found to be a short polypeptide of 42 to 43 amino acids. This information led to cloning of amyloid precursor protein (APP), a much larger protein of more than 700 amino acids which is widely expressed by neurons throughout the brain in normal individuals as well as in those with AD. The function of APP is unknown, although the structural features of the protein suggest that it may serve as a cell surface receptor for an as-yet-unidentified ligand. The production of β-amyloid from APP appears to result from abnormal proteolytic cleavage of APP (Selkoe, 1993; Ashall and Goate, 1994).

Analysis of APP gene structure in pedigrees exhibiting autosomal dominant inheritance of AD has shown that in some families mutations of the β-amyloid-forming region of APP are present, while in others mutations of proteins involved in the processing of APP have been implicated (Clark and Goate, 1993). These results demonstrate that it is possible for abnormalities in APP or its processing to cause AD. The vast majority of cases of AD, however, are not familial, and in these sporadic cases of AD structural abnormality of APP or related proteins has not been observed consistently. Although these observations suggest that agents that alter the metabolism of APP might alter the course of AD in both familial and sporadic cases (Whyte *et al.*, 1994), no clinically practical strategies have been developed yet.

Treatment of Alzheimer's Disease. A major approach to the treatment of AD has involved attempts to augment the cholinergic function of the brain (Johnston, 1992). An early approach was the use of precursors of acetylcholine synthesis, such as *choline chloride* and *phosphatidyl choline (lecithin).* Although these supplements are generally well tolerated, randomized trials have failed to demonstrate any clinically significant efficacy. Direct intracerebroventricular injection of cholinergic agonists such as bethanacol appears to have some beneficial effects, although this requires surgical implantation of a reservoir connecting to the subarachnoid space and is too cumbersome and intrusive for practical use. A somewhat more successful strategy has been the use of inhibitors of acetylcholinesterase (AChE), the catabolic enzyme for

acetylcholine (*see* Chapter 8). *Physostigmine,* a rapidly acting, reversible AChE inhibitor, produces improved responses in animal models of learning, and in patients with AD some studies have demonstrated mild transitory improvement in memory following physostigmine treatment. The use of physostigmine has been limited because of its short half-life and tendency to produce symptoms of systemic cholinergic excess at therapeutic doses.

Recently, the acridine derivative *tacrine* (COGNEX, 1,2,3,4-tetrahydro-9-aminoacridine) has been approved by the United States Food and Drug Administration for the treatment of dementia in AD. Tacrine was first synthesized nearly 50 years ago, and the pharmacology of this agent has been the subject of numerous studies (Freeman and Dawson, 1991). It is a potent centrally acting inhibitor of AChE (*see* Chapter 8). A trial reported in 1986 described clinical efficacy of intravenous tacrine in AD, although subsequent review of the data from this trial revealed methodological flaws (Summers *et al.,* 1986; Food and Drug Administration, 1991). Three later studies of oral tacrine in combination with lecithin confirmed that tacrine does affect some measures of memory performance (Chatellier and Lacomblez, 1990; Gauthier *et al.,* 1990; Eagger *et al.,* 1991), but the magnitude of improvement observed with the combination of lecithin and tacrine was modest at best. In two of the studies, the improvements in cognitive scores were judged to be clinically insignificant; in the third, modest improvement in some measurements was observed, the clinical relevance of which was deemed to be a matter of individual physician judgement (Eagger *et al.,* 1991). The side effects of tacrine may be significant and dose-limiting: abdominal cramping, nausea, vomiting, and diarrhea were observed in up to one-third of patients receiving therapeutic doses. Tacrine also may cause hepatotoxicity, as evidenced by the elevation of serum transaminases observed in up to 20% of patients treated; these elevations usually resolve rapidly if treatment is discontinued. Because of the relatively small improvement that results from tacrine treatment and the significant side-effect profile, its clinical usefulness is limited (Growdon, 1992).

HUNTINGTON'S DISEASE

Clinical Features. HD is a dominantly inherited disorder characterized by the gradual onset of motor incoordination and cognitive decline in mid-life. Symptoms develop insidiously, either as a movement disorder manifested by brief jerk-like movements of the extremities, trunk, face, and neck (chorea), or personality changes, or both. Fine motor incoordination and impairment of rapid eye movements are early features. Occasionally, especially when the onset of symptoms occurs before the age of 20, choreic movements are less prominent, and, instead, bradykinesia and dystonia predominate. As the disorder progresses, the involuntary movements become more severe, dysarthria and dysphagia develop, and balance is impaired. The cognitive disorder manifests itself first by slowness of mental processing and difficulty in organizing complex tasks. Memory is affected, but affected persons rarely lose their memory of family, friends, and immediate situation. Such persons often become irritable, anxious, and depressed. Less frequently, paranoia and delusional states are manifest. The outcome of HD is invariably fatal; over a course of 15 to 30 years, the affected person becomes totally disabled and unable to communicate and requires full-time care; death ensues from the complications of immobility (Hayden, 1981; Harper, 1991, 1992).

Pathology and Pathophysiology. HD is characterized by prominent neuronal loss in the caudate/putamen of the brain (Vonsattel *et al.,* 1985). Atrophy of these structures proceeds in an orderly fashion, first affecting the tail of the caudate nucleus and then proceeding anteriorly, from medial–dorsal to lateral–ventral. Other areas of the brain also are affected, although much less severely; morphometric analyses indicate that there are fewer neurons in cerebral cortex, hypothalamus, and thalamus. Even within the striatum, the neuronal degeneration of HD is selective. Interneurons and afferent terminals are largely spared, while the striatal projection neurons (the medium spiny neurons) are severely affected. This leads to large decreases in striatal GABA concentrations, whereas somatostatin and dopamine concentrations are relatively preserved (Ferrante *et al.,* 1987; Reiner *et al.,* 1988).

Selective vulnerability also appears to underlie the most conspicuous clinical feature of HD, the development of chorea. In most adult-onset cases, the medium spiny neurons that project to LGP and SNpr (the indirect pathway) appear to be affected earlier than those projecting to the MGP (the direct pathway; Albin *et al.;* 1990, 1992). The disproportionate impairment of the indirect pathway increases excitatory drive to the neocortex, producing involuntary choreiform movements (Figure 22–9). In some individuals, rigidity rather than chorea is the predominant clinical feature; this is especially common in juvenile-onset cases. In these cases the striatal neurons giving rise to both the direct and indirect pathway are impaired to a comparable degree.

Genetics. HD is an autosomal dominant disorder with nearly complete penetrance. The average age of onset is between 35 and 45 years, but the range varies from as early as age 2 years to as late as the mid-80s. Although the disease is inherited equally from mother and father, more than 80% of those developing symptoms before the age of 20 inherit the defect from the father. Known homozygotes for HD show clinical characteristics identical to the typical HD heterozygote, indicating that the unaffected chromosome does not attenuate the disease symptomatology. Until the discovery of the genetic defect responsible for HD, *de novo* mutations causing HD were thought to be unusual, and because the disease could present late in life, the occurrence of a new mutation was difficult to prove on clinical grounds alone.

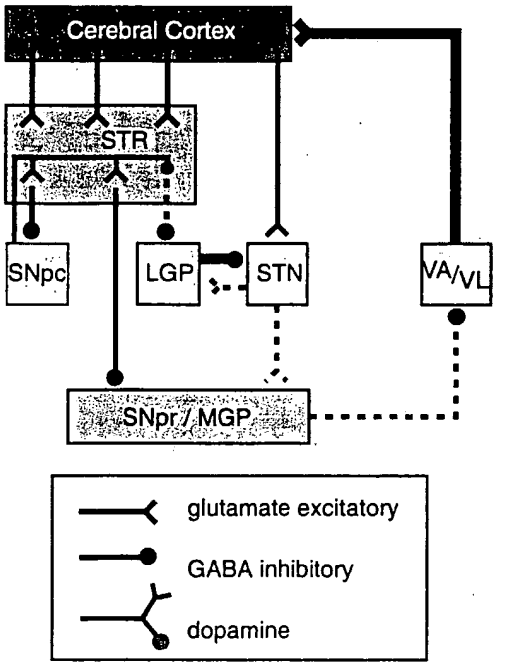

Figure 22–9. The basal ganglia in Huntington's disease (HD).

HD is characterized by loss of neurons from the STR. The neurons that project to the LGP and form the indirect pathway are affected earlier in the course of the disease than those that project to the MGP. This leads to a loss of inhibition of the LGP. The increased activity in this structure in turn inhibits the STN, SNpr, and MGP, resulting in a loss of inhibition to the VA/VL thalamus and increased thalamocortical excitatory drive. Thin line, normal pathway activity; thick line, increased pathway activity in HD; dashed line, reduced pathway activity in HD. (*See* legend to Figure 22–6 for definitions of anatomical abbreviations.)

In 1983, Gusella and co-workers identified a marker, D4S10, that was closely linked to the *HD* gene on chromosome 4 (Gusella *et al.*, 1983). After an arduous ten-year multi-investigator collaborative effort, a region near the telomere of chromosome 4 was found to contain a polymorphic $(CAG)_n$ trinucleotide repeat that was significantly expanded in virtually all individuals with HD (Huntington's Disease Collaborative Research Group, 1993). The expansion of this trinucleotide repeat is the genetic alteration responsible for HD. The range of CAG repeat length in normal subjects is between 9 and 34 triplets, with a median repeat length on normal chromosomes of 19. The repeat length in *HD* varies from 38 to over 100. At the current time, the significance and clinical effects of repeat lengths in the range of 35 to 39 are not known, and presymptomatic testing protocols must take this unknown variable into consideration. Repeat length is correlated inversely with age of onset. The younger the age of onset, the higher the probability of a large repeat number. This correlation is strongest in individuals with onset before the age of 30, while above the age of 30 the correlation is weaker; thus, repeat length cannot serve as an adequate predictor of age of onset in most individuals.

Selective Vulnerability. The mechanism by which the expanded trinucleotide repeat leads to the clinical and pathological features of HD is unknown. The HD mutation lies within a gene designated *IT15*. The *IT15* gene itself is very large (10 kilobases) and is thought to encode a protein of approximately 348 kDa or 3144 amino acids. The predicted protein, huntingtin, does not resemble any known protein. The trinucleotide repeat, which encodes the amino acid glutamine, occurs at the 5′-end of *IT15* and is followed directly by a second, shorter repeat of $(CCG)_n$ which encodes the amino acid proline. The *HD* gene is expressed widely throughout the body. High levels of expression are present in brain, pancreas, intestine, muscle, liver, and adrenals. Very high levels of expression were observed in testes. In brain, expression of *IT15* does not appear to be correlated with neuron vulnerability; although the striatum is most severely affected, neurons in all regions of the brain express similar levels of *IT15* mRNA (Landwehrmeyer *et al.*, 1994).

The ability of the HD mutation in *IT15* to produce selective neural degeneration despite nearly universal expression of the gene among neurons may be related to metabolic or excitotoxic mechanisms. HD patients tend to be thin, suggesting the presence of a systemic disturbance of energy metabolism. In animal models, injection into the striatum of agonists for the NMDA subtype of excitatory amino acid receptor can cause pathology similar to that seen in HD (Beal *et al.*, 1986). More interesting, however, is the fact that inhibitors of Complex II of the mitochondrial respiratory chain also can result in HD-like striatal lesions—even when given systematically (Beal *et al.*, 1993). Furthermore, this pathology can be diminished by NMDA receptor antagonists, suggesting that this is an example of a metabolic impairment giving rise to excitotoxic neuronal injury. Studies employing magnetic resonance spectroscopy have provided direct evidence of an alteration in energy metabolism in HD *in vivo* (Jenkins *et al.*, 1992). Thus, the link between the widespread expression of the gene for the abnormal IT15 protein in HD and the selective vulnerability of neurons in the disease may arise from the interaction of a widespread defect in energy metabolism with the intrinsic properties of striatal neurons, including their capacity and need for oxidative metabolism as well as the types of glutamate receptors present. This hypothesis has a number of potentially important therapeutic implications, for it is unlikely that it will be possible in the near future to correct the genetic defect in the brains of individuals with HD, but it may be possible to develop agents that alter metabolic function or protect against excitotoxic injury and thereby arrest or modify the course of the disease.

Symptomatic Treatment of Huntington's Disease. Practical treatment for symptomatic HD emphasizes the selective use of medications (Shoulson, 1992). No current medication slows the progression of the disease, and many medications can impair function because of side effects. Treatment is needed for patients who are depressed, irritable, paranoid, excessively anxious, or psychotic. Depression can be treated effectively with standard antidepressant drugs with the caveat that those drugs with substantial anticholinergic profiles can exacerbate chorea. *Fluoxetine* (Chapter 19) is effective treatment for both the depression and the irritability manifest in symptomatic HD. *Carbamazepine* (Chapter 20) has also been found to be effective for depression. Paranoia, delusional states, and psy-

chosis usually require treatment with neuroleptics, but the doses required often are lower than those usually used in primary psychiatric disorders. These agents also reduce cognitive function and impair mobility and thus should be used in the lowest doses possible and be discontinued when the psychiatric symptoms are resolved. In individuals with predominantly rigid HD, *clozapine* (Chapter 18) or carbamazepine may be more effective for treatment of paranoia and psychosis.

The movement disorder of HD *per se* only rarely justifies pharmacological therapy. For those with large-amplitude chorea causing frequent falls and injury, dopamine-depleting agents such as *tetrabenazine* or *reserpine* (Chapter 33) can be tried, although patients must be monitored for hypotension and depression. Neuroleptics also can be used but these often do not improve overall function because they decrease fine motor coordination and increase rigidity. Many HD patients exhibit worsening of involuntary movements as a result of anxiety or stress. In these situations, judicious use of sedative or anxiolytic benzodiazepines can be very helpful. In juvenile-onset cases where rigidity rather than chorea predominates, dopamine agonists have had variable success in the improvement of rigidity. These individuals also occasionally develop myoclonus and seizures that can be responsive to *clonazepam, valproic acid,* or other anticonvulsants.

AMYOTROPHIC LATERAL SCLEROSIS

Clinical Features and Pathology. ALS is a disorder of the motor neurons of the ventral horn of the spinal cord and the cortical neurons that provide their afferent input. The ratio of males to females affected is approximately 1.5:1 (Kurtzke, 1982). The disorder is characterized by rapidly progressive weakness, muscle atrophy and fasciculations, spasticity, dysarthria, dysphagia, and respiratory compromise. Sensory function generally is spared, as is cognitive, autonomic, and oculomotor activity. ALS usually is progressive and fatal, with most affected patients dying of respiratory compromise and pneumonia after 2 to 3 years, although occasional individuals have a more indolent course and survive for many years. The majority of cases are sporadic although autosomal dominant and autosomal recessive inheritance has been described in several kindreds. The pathology of ALS corresponds closely to the clinical features: there is prominent loss of the spinal and brainstem motor neurons that project to striated muscles (although the oculomotor neurons are spared) as well as loss of the large pyramidal motor neurons in layer V of motor cortex which are the origin of the descending corticospinal tracts. In familial cases, Clarke's column and the dorsal horns are sometimes affected (Caroscio *et al.,* 1987; Rowland, 1994).

Etiology. The cause of the motor neuron loss in ALS is unknown, but theories include autoimmunity, excitotoxicity, free radical toxicity, and viral infection (Rowland, 1994). Recent studies in a subset of families with autosomal dominant ALS have provided interesting clues. Mutations in the gene for the enzyme superoxide dismutase (SOD) have been identified in affected members of several kindreds and in additional sporadic cases (Rosen *et al.,* 1993). This enzyme is thought to have an important role in the metabolism of potentially neurotoxic free radicals. SOD activity is normal or decreased in spinal cord and cerebrospinal fluid of patients with ALS. Animals transgenic for normal human SOD express excess SOD activity and do not develop motor neuron disease (Przedborski *et al.,* 1992). In fact, these animals have reduced susceptibility to the free-radical–mediated toxic effects of hypoxia/ischemia. Animals transgenic for the human SOD gene containing the mutations observed in ALS do develop progressive motor neuron disease. The relationship between the mutation of SOD and selective vulnerability of spinal motor neurons is an area of active investigation. Based on the SOD mutations observed in ALS, trials of free radical scavengers and SOD replacement therapy are in progress.

Alternative theories of selective neuronal degeneration in ALS include the hypothesis that glutamate reuptake may be abnormal, leading to accumulation of glutamate and excitotoxic injury. Studies of ALS tissue and CSF suggest that tissue glutamate levels and glutamate reuptake are decreased, whereas CSF glutamate levels are increased (Rothstein *et al.,* 1992). Based on these observations, several trials of glutamate antagonists in ALS, including *dextromethorphan, lamotrigine,* and branched-chain amino acids, have been initiated, but so far have proven negative (Testa *et al.,* 1989; Askmark *et al.,* 1993; Eisen *et al.,* 1993). Neural growth factors also are under study to slow the loss of neurons in ALS (Sendtner *et al.,* 1992). An agent that blocks glutamate release, *riluzole,* has been reported to delay death and the need for tracheostomy in patients with bulbar-onset ALS but not in patients with spinal-onset ALS; a larger study is now in progress (Bensimon *et al.,* 1994). Glutamate receptors may eventually prove to be important targets of agents to slow or arrest the progression of ALS.

Spasticity and the Spinal Reflex. Spasticity is an important component of the clinical features of ALS, in that the presence of spasticity often leads to considerable pain and discomfort and reduces mobility, which is already compromised by weakness. Furthermore, spasticity is the feature of ALS which is most amenable to present forms of treatment. *Spasticity* is defined as an increase in muscle tone characterized by an initial resistance to passive displacement of a limb at a joint followed by a sudden relaxation (the so-called clasped-knife phenomenon). Spasticity is the result of the loss of descending inputs to the spinal motor neurons, and the character of the spasticity depends on which nervous system pathways are affected (Davidoff, 1990). Whole repertoires of movement can be generated directly at the spinal cord level; it is beyond the scope of this chapter to describe these in detail. The monosynaptic tendon-stretch reflex is the simplest of the spinal mechanisms contributing to spasticity. Primary Ia afferents from muscle spindles, activated when the muscle is rapidly stretched, synapse directly on motor neurons going to the stretched muscle, causing it to contract and resist the movement. A collateral of the primary Ia afferent synapses on a "Ia-coupled in-

terneuron" that inhibits the motor neurons innervating the antagonist of the stretched muscle, allowing the contraction of the muscle to be unopposed. Upper motor neurons from the cerebral cortex (the pyramidal neurons) suppress spinal reflexes and the lower motor neurons indirectly by activating the spinal cord inhibitory interneuron pools. The pyramidal neurons use glutamate as a neurotransmitter. When the pyramidal influences are removed, the reflexes are released from inhibition and become more active, leading to hyperreflexia. Other descending pathways from brainstem also influence spinal reflex activity including the rubro-, reticulo-, and vestibulospinal pathways and the descending catecholamine pathways. When just the pyramidal pathway is affected, extensor tone in the legs and flexor tone in the arms are increased. When the vestibulospinal and catecholamine pathways are impaired, increased flexion of all extremities is observed and light cutaneous stimulation can lead to disabling whole-body spasms. In ALS, pyramidal pathways are impaired with relative preservation of the other descending pathways, resulting in hyperactive deep-tendon reflexes, impaired fine motor coordination, increased extensor tone in the legs, and increased flexor tone in the arms. The gag reflex often is overactive as well.

Symptomatic Therapy. Symptomatic therapy for ALS has focused on the treatment of spasticity. For increased extensor tone and clonus, the $GABA_B$ agonist *baclofen* (LIORESAL) has proved to be the most effective agent. Initial doses of 5 to 10 mg a day are recommended, but the dose can be increased to as much as 200 mg a day if necessary. If weakness occurs, the dose should be lowered. Benzodiazepines and other muscle relaxants have little effect. Treatment also may include antidepressant medication and medication for salivation in the bulbar form of ALS *(oxybutynin, trihexyphenidyl, amitriptyline).*

PROSPECTUS

Although advances in the symptomatic therapy of the neurodegenerative disorders, particularly PD, has improved the lives of many patients, the goal of current research is to develop treatments that can prevent, retard, or reverse neuronal cell death. Promising areas for drug development are the mechanisms implicated in several of the disorders: excitotoxicity, defects in energy metabolism, and oxidative stress. Glutamate antagonists have great potential, but their use is limited by the relatively nonselective activity of the available agents. Increased knowledge of the structure and function of glutamate receptor subtypes should make more selective and useful agents available. Pharmacological reduction of oxidative stress also is feasible, despite the disappointing results of initial clinical trials with tocopherol and selegiline. Neural growth factors are another important area for drug development. Several factors that promote the differentiation of neurons and the establishment of neural connections during development have been identified, and these may eventually prove useful in retarding or reversing neuronal death. A more direct and currently accessible approach to reversing neuronal loss is surgical transplantation of neurons; this has been accomplished in PD with a moderate degree of success and has been proposed as a treatment for other conditions such as AD. In addition to these general approaches to neurodegeneration, more specific treatments for the various diseases should become feasible with advances in knowledge of their etiology. For example, discovery of the role of β-amyloid in AD has sparked the study of agents that alter its synthesis, while discovery of the function of the HD gene is likely to lead to novel treatment strategies for that disorder.

For further information regarding neurodegenerative diseases for which the drugs discussed in this chapter are useful, the reader is referred to the following chapters in *Harrison's Principles of Internal Medicine,* 13th ed., McGraw-Hill, New York, 1994: Parkinson's disease, Chapter 371; Alzheimer's disease and Huntington's disease, Chapter 370; and amyotrophic lateral sclerosis, Chapter 372.

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Motor deficiency in Parkinson's disease

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Abstract. The basal ganglia comprise a group of gray matter structures beneath the cerebral cortex, that surrounds the thalamus and hypothalamus. The basal ganglia play an important role in controlling movement. The motor circuits within the striato-pallidal complex are thought to facilitate desired movement and inhibit unwanted movement through their influence, via the thalamus, mainly on cortical precentral motor regions. Localized damage to parts of the basal ganglia occurs in certain diseases such as Parkinson's disease. Parkinsonism is a common neurological disorder that affects about one person in every 1,000 of the general population and about 2% in the elderly. The diagnosis of Parkinson's disease is based on the presence of two or more of the major symptoms: tremor, rigidity, postural instability, and bradykinesia. The pathological process behind the motor disabilities of Parkinsonism is a progressive degeneration of dopaminergic neurons of the substantia nigra, that results in dopamine depletion in the striatum. Brain dopamine deficiency is sufficient to explain all of the major symptoms of Parkinson's disease.

Key words: Parkinson's disease, basal ganglia, motor control, tremor,

PATHONEUROPHYSIOLOGY OF MOTOR DEFICIT IN PARKINSON'S DISEASE

The basal ganglia comprise a group of gray matter structures beneath the cerebral cortex, that surrounds the thalamus and hypothalamus. Details of their anatomy and physiology have been well documented (Carpenter 1981, DeLong and Georgopoulos 1981, Horynkiewicz 1981, Graybiel 1984, Young and Penney 1984, 1988, Lange et al. 1997). It is generally accepted that the basal ganglia are responsible for modulating and facilitating various motor and cognitive programs, although mechanisms of these processes are still unknown (Young and Penney 1988).

Localized damage to parts of the basal ganglia occurs in certain diseases such as Parkinson's disease (PD), Wilson's disease, and Huntington's chorea. The extent of the damage varies from patient to patient, so that each shows his own pattern of symptoms. In his "Essay on Shaking Palsy" James Parkinson (1817) focused on postural and gait deficits: ... the patient is found to be less strict than usual in preserving an upright posture... and "Involuntary tremulous motion, with lessened muscular power, in parts not in action and even when supported; with a propensity to bend the trunk forwards, and to pass from a walking to a running pace; the senses and intellect being uninjured" (Barbeau 1986).

Parkinsonism is a common neurological disorder; it affects about one person in every 1,000 of the general population and about 2% in the elderly (Peterson et al. 1988). The diagnosis of Parkinson's disease is based on the presence of two or more of the major symptoms: tremor, rigidity, postural instability, and bradykinesia. Other signs and symptoms of PD include seborrhoea, intolerance of heat, edema, cyanosis, increased salivation, decreased rate of swallowing. These will not be discussed in this paper.

The pathological process behind the motor disabilities of PD is a progressive degeneration of dopaminergic neurons of the substantia nigra, that results in dopamine depletion in the striatum. Brain dopamine deficiency is sufficient to explain all of the major symptoms of PD (Marsden 1982, 1984, for review see Narabayashi 1995). In early stages of parkinsonism, there appears to be a compensatory increase in the number of dopamine receptors to accommodate the initial loss of dopamine neurons (Ebadi et al. 1996). As the disease progresses, the number of dopamine receptors decreases, apparently due to the concomitant degeneration of dopamine target sites on striatal neurons.

The basal ganglia play an important role in controlling movement. The motor circuits within the striato-pallidal complex are thought to facilitate desired movement and inhibit unwanted movement through their influence, *via* the thalamus, mainly on cortical precentral motor regions (Marsden and Obeso 1994). In patients with Parkinson's disease stereotaxic lesions directed at the motor thalamus improve rigidity and tremor and do not worsen parkinsonian hypokinesia and bradykinesia. The motor circuits of the basal ganglia are part of a distributed motor system which can operate, albeit imperfectly, in the absence of striato-pallido-thalamo-cortical feed--back. It seems most likely that a pause in firing of medial pallidal and substantia nigra reticulata neurons permits movements generated by cortical motor areas. An increase in firing of medial pallidal neurons, which so far has been the major focus of attention, may be more concerned with inhibition of unwanted movement.

A change in firing of medial pallidal neurons appears to occur too late to initiate a new movement. However, the motor circuit within the striato-pallidal system routinely receives a continuous delayed read-out of cortical motor activity and issues an output directed *via* the thalamus mainly to premotor cortical regions. This may permit the routine automatic execution of sequences of movements generated in cortical motor areas. There is evidence that other regions of the striatum respond to significant external or internal cues as dictated by their cortical inputs, the significance being determined by memory, novelty, emotional and other contexts. Such events capture the attention of the non-motor striatum, which then interrupts the routine operation of the motor circuit, perhaps at the level of the medial pallidum and substantia nigra pars reticulata, to permit new cortical motor action.

The function of the basal ganglia has also been examined in terms of changes in behavior caused by pathology, as in PD (Marsden 1985, Roos et al. 1996). The observations of poorer concept formation (Bowen et al. 1975, Flowers and Robertson 1985), impairment in learning (Frith et al. 1986, Verschueren et al. 1997), poorer attentional processes (Lee and Smith 1983, Cools et al. 1984), as well as depression (Dakof and Mendelsohn 1986, Gotham et al. 1986, Taylor et al. 1986) in PD patients suggest that the basal ganglia are also involved in higher cognitive functions. Impairments in these cognitive factors may also affect movement performance (Jordan et al. 1992b).

TREATMENT STRATEGIES

The major motor disturbances in Parkinson's disease are thought to be caused by overactivity of the internal segment of the globus pallidus, in large part due to excessive drive from the subthalamic nucleus. The excessive inhibitory activity of the globus pallidus is thought to inhibit the motor thalamus and the cortical motor system thus producing the slowness, rigidity, and poverty of movement characteristic of parkinsonian states. Pallidotomy and thalamotomy are the stereotactic procedures most commonly performed in PD patients who fail to obtain satisfactory relief of their symptoms with drug therapy. Small lesions disrupt the abnormal activity of basal ganglia circuitry (Nakamura et al. 1979, Jankovic et al. 1995, Lozano et al. 1995, Baron et al. 1996, Kraus and Jankovic 1996). Therefore, pallidotomy enhances motor performance, reduces akinesia, improves gait, and almost completely eliminates levodopa-induced dyskinesias (Lozano et al. 1995).

Fetal nigral transplantation, which is still an experimental procedure, has the potential for restoring the lost nigrostriatal pathway (Krauss and Jankowic 1996). Also a new experimental procedure, external application of picoTesla range magnetic fields has been reported recently to be efficacious in the treatment of Parkinson's disease (Sandyk and Derpapas 1993). Improvement with magnetic therapy was noted not only in the motor control (gait, postural instability) but also in nonmotor aspects of the disease including mood, anxiety, autonomic and cognitive functions.

MOTOR DEFICITS IN PARKINSONISM

The impairment of motor functions observed in PD patients may be considered to consist of a primary deficit - so called negative symptoms including poverty of movement and impairment of postural reflexes, and secondary defects - positive symptoms such as rigidity and tremor (Knutson and Martensson 1986). When executing a repetitive motor task, parkinsonians have difficulties in maintaining an unchanged speed and amplitude of the individual movements. In walking, for instance, there is a tendency for individual steps to become shorter and eventually come to a complete stop (Morris et al. 1994). The gait may become arrested by even the smallest obstacle (Stern et al. 1980, 1983a). Generally, any sensory stimuli may markedly affect motor performance (Knutson and Martensson 1986, Morris et al. 1994). If walking is stopped by a sensory stimulus and stress and anxiety is added, the patient may not be able to start locomotion again for a long period. In some patients the problem of gait may be overcome by various external cues. Speech defects are common in advanced PD and include disturbances in respiration, phonation and articulation. These problems have also attracted the attention of some motor control researchers (Stewart et al. 1995).

TREMOR

Tremor at rest is a cardinal sign of Parkinson's disease. Some patients have only a resting tremor for at least 5 years without developing other parkinsonian signs or symptoms. Recent findings suggest the existence of a separate subtype of the disease, namely, tremulous Parkinson's disease in which there is a resting tremor alone (Chang et al. 1995). Tremor can also be a manifestation of Wilson's disease, lesions of the cerebellum and midbrain, peripheral neuropathy, trauma, alcohol, and conversion disorders (Anouti and Koller 1995).

The origin of the PD tremor is still uncertain. Patients with PD are reported to have tremor predominantly in their hands, feet, and chin (Jankovic and Frost 1981). Electromyographic recordings show rhythmic activity alternating in antagonistic muscles at a frequency range between 3.5 and 7 Hz (Hagbarth et al. 1975, Shahani and Young 1976, Findley et al. 1981, Delwaide and Gonce 1988, Marsden 1992, Koller et al. 1994, Anouti and Koller 1995, Palmer and Hutton 1995, Volkman et al. 1996). The tremor frequency can differ between the upper and lower limbs, and even between the two upper limbs (Delwaide and Gonce 1988).

Rhythmically alternating contractions of a given muscle group and its antagonists are organized as normal movements with alpha-gamma coactivation (Hagbarth et al. 1975). The motor units, however, respond with abnormal clusters of action potentials - so called doublets and triplets (Young and Shahani 1979, Young 1985). What is more important, within the muscles themselves, the motor units are firing in a synchronous manner at regular intervals (Barbeau 1986). During an active muscle contraction the synchronized firing is lost and most PD patients show no other tremor. However, the tremor in the arms may still be present when walking, and when performing a repetitive arm abduction-adduction task (Jankovic and Frost 1981). Young (1985) has

found that when patients are asleep and activate their axial muscles to shift position, tremor can start and awaken them.

The PD tremor is increased by nervousness or fatigue and may disappear in sleep. It can be also suppressed by relaxation of the axial postural muscles (Delwaide and Gonce 1988). It may be completely absent when the subject is concentrating on some skilled task. PD resting tremor in the arms and legs responds to the use of anticholinergics and a combination of carbidopa and levodopa.

A variety of clinical and experimental findings suggest that parkinsonian resting tremor results from the involuntary activation of a central mechanism normally used for the production of rapid voluntary alternating movements. Magnetic field tomography studies showed that tremor in PD is indeed accompanied by rhythmic subsequent neural activation at the diencephalic level and in lateral premotor, somatomotor, and somatosensory cortex (Volkman et al. 1996).

Microelectrode recordings from the thalamus of PD patients revealed rhythmic neuronal activity associated with contralateral limb tremor (Jasper and Bertrand 1964, Albe-Fessard et al. 1966, Narabayashi and Ohye 1983). Some of this activity is simply being driven by muscle afferents but some neurons exhibit their own rhythmical activity (for review see Delwaide and Gonce 1988). Lee and Stein (1981) found neurons within the basal ganglia and the thalamus of PD patients that fire at the same frequency as the tremor, and hypothesized that damage to the inhibitory pathway between the substantia nigra pars reticulata and the striatum may lead to excessive striatal excitatory output facilitating oscillating bursts of activity in the thalamus. The tremogenic thalamic pacemaker would be included in a long hyperactive neuronal loop starting from the muscle spindles and going up to the thalamus, the motor cortex and returning to the muscular level via the pyramidal track (Delwaide and Gonce 1988).

Some physiological observations also support the theory that Parkinson tremor is a centrally driven rhythm that may be influenced by feedback effects. There is, for example, in PD patients a significant correlation between the peak of acceleration and the peak of rectified electromyographic activity from the muscle responsible for finger extension (Palmer and Hutton 1995). Such a correlation is not seen in age-matched control subjects.

The quality of motor control is affected by the tremor. Typically, the increase in the involuntary oscillations result in both a decline in sensory sensitivity, and in delayed movement initiation. Some patients with parkinsonism are not able to use visual information in a normal manner in a simple motor tracking task. The pathological tremor present in these individuals acts as noise and prevents them from performing normally (Vasilakos and Beuter 1993). On the other hand, a systematic phase relationship between tremor-at-rest and the onset of voluntary motor responses in PD has been recently documented (Wierzbicka et al. 1993, Staude et al. 1995). Reaction times of PD patients exhibit a significant dependence of mean values and variability on the current tremor phase at the onset of the voluntary motor response. Responses with an onset of contraction during the beginning of an EMG tremor burst are substantially delayed (on average 50 ms) and show more variability in comparison to responses initiated at later times in the tremor cycle. This effect can be explained by a simple gating process splitting the tremor cycle into two different system states that support or inhibit the initiation of voluntary motor responses (Wierzbicka et al. 1993).

Chronic thalamic stimulation, involving permanent implantation of deep brain electrodes and a pulse generator, effectively controls contralateral tremor (Benabid et al. 1996). It interesting that a low frequency (50 Hz) electrical stimulation of the ventral intermediate thalamic nucleus may increase tremor, while stimulation with a frequency greater than 100 Hz leads to suppression of the tremor (Alesch et al. 1995). The patient's ability to generate steady torque and rapid movements is also improved with moderate and high frequency stimulation (Pfann et al. 1996). However, even with motor improvements and with a decrease of tremor muscular activity abnormalities typical for PD remain.

RIGIDITY

Rigidity is manifested by increased resistance to passive movement throughout the range of motion of a joint. It is typically independent on movement velocity and is often described as "lead-pipe" rigidity; it persists as long as the stretch is maintained. The resistance to forced movement of the limb fluctuates in a jerky fashion and thus the rigidity may be regularly interrupted at a frequency of 5 to 6 Hz (cogwheel phenomenon).

The rigidity may affect the limbs, trunk, neck and other group of muscles. For example the characteristic immobile mask-like face of PD patients results from rigidity. PD rigidity differs from the rigidity of decerebra-

tion in that the force of resistance does not typically depend on the speed of displacement. In some patients however, the resistance to stretch is inversely proportional to velocity, being greatest when movement is slow (Delwaide and Gonce 1988). Both voluntary contraction and passive mobilization of the contralateral limb reinforce rigidity. Generally, reinforcement maneuvers are more affective if achieved by proximal rather than distal muscles and in a standing rather than a seated position (Delwaide and Gonce 1988). The latter observation indicates a role in rigidity of descending pathways, especially of the vestibulospinal tract.

Physiologically the only undisputed fact is that a dorsal root section reduces rigidity, evidencing that afferent input from joint, muscle, or cutaneous receptors is a contributing factor. A stereotaxic lesion within the ventrolateral nucleus of the thalamus, on the other hand, eliminates rigidity (Narabayashi 1985). Since the ventrolateral nucleus of the thalamus receives pallidal afferent inputs, rigidity in PD is interpreted as dysfunction of pallidal neurons caused by dopamine deficiency within the striatum (Narabayashi 1985).

Despite of a fact that there are well documented changes in Ia spinal interneuron activity in PD (Day et al. 1981), most authors advocate a concept of an increased long-loop reflex to explain rigidity (Mortimer and Webster 1978, Evarts and Vaughn 1981, Berardelli et al. 1983,1996, Dietz et al. 1988). The long-loop reflexes are commonly studied using limb or posture perturbation experimental models. In response to a movement perturbation, a sequence of three EMG bursts (M1-M3) appears in the muscle activity (Tatton et al. 1975, for review see Dienner and Dichgans 1986). The first of these corresponds to the stretch reflex (Lee and Tatton 1975) and is of normal amplitude in parkinsonians. The M2 burst involving supraspinal loop is significantly increased in PD rigidity.

POSTURAL INSTABILITY AND ABNORMALITIES

The parkinsonian posture is described in general as a "stooped posture" (Knuttson 1972, Murray et al. 1978, Barbeau 1986, Andrews 1987, Koozekanani et al. 1987, Beckley et al. 1991, Kitamura et al. 1991). The neck and head of PD patients are inclined forward. Their trunk is flexed forward and the dorsal spine shows kyphosis. The arms of parkinsonians are slightly abducted, the elbows are flexed and the hands are carried in front of the body with the fingers partially flexed. The hips and knees are flexed, and the ankle dorsiflexion angle decreases as the disability increases which causes the PD patients to stand more on their toes (Andrews 1987, Schieppati and Nardone 1991, Yekutiel 1993).

An important point made by Martin (1967) is that postural changes do not result from muscular weakness. Dietz et al. (1981) extended this observation to gait. Moreover, Martin stressed that the deficit in postural adjustment appears in the face of a dynamic perturbation such as tilt. These observations have been confirmed in a study by Traub and coworkers (1980). The postural impairment is not simply loss of planning or coordination, but rather a bias towards specific posture and gait (Calne et al. 1985).

Postural instability is one of the most disabling features of Parkinson's disease (Beckley et al. 1991, Bloem 1992). Many factors contribute to balance impairment of Parkinson patients, including disturbed postural reflexes and poor control of voluntary movement. Additional factors which place Parkinson patients at risk for falls are side-effects of medication (dyskinesias), gait abnormalities, muscular weakness in leg muscles and superimposed age-related changes such as reduced peripheral sensation.

Anticipatory postural adjustments, and postural reflexes are disturbed in Parkinson's disease (Traub et al. 1980). Studies of anticipatory postural adjustments show that parkinsonians have difficulty simultaneously performing two separate motor programs (Benecke et al. 1986), and they have also difficulty switching from one motor program to another (Benecke et al. 1987). This has led researchers like Rogers et al. (1987) to believe that the basal ganglia may play a role in linking the prime mover and postural components in balance control.

Andrews (1987) claims that vestibular control of posture is affected by damage to the basal ganglia. Since the proprioception from the neck is also impaired due to rigidity, both deficits would result in the decline of the vertical perception which the basic element of postural control. Thus it may lead to postural abnormality and postural instability due to impaired control of the center of gravity (Calne et al. 1985).

Results of studies of reflex postural responses are very controversial, but most agree that PD patients respond differently than controls. Some authors assume that peripheral and spinal mechanisms such as muscle spindles (Burke et al. 1977), and patterns of reciprocal inhibition (Obeso et al. 1985) function normally in PD subjects

amidst a higher level of background activity, suggesting that Parkinsonism is the result of hyperactivity in transcortical loops (Lakke et al. 1982, Delwaide 1985, Cody et al. 1986). Although the patterns of muscle innervation are correct, their anticipatory adjustments (Calne et al. 1985), and initiatory processes (Hallett et al. 1977) are impaired, with the prepared response falling short of what is required (Hallett and Khoshbin 1980). These authors have taken the position that spinal reflex activity in the muscles of PD patients is no different from those of normal tensed muscles, and that the problems most likely lie with transcortical loops. Delwaide et al. (1993) suggest however, that at least two spinal mechanisms behave abnormally in PD due to changes in the activity of descending spinal tracks. Increased excitability of Ia inhibitory spinal interneuron was associated with reduced excitability of Ib interneuron suggesting that the changes are due to the same mechanism. The reticulospinal tract appears to be mostly responsible for these changes. These changes may be seen in increased tendon jerks which are a feature of idiopathic parkinsonism. In most cases there is no correlation of reflex score such as in the tendon jerk with the severity of PD or with its cardinal signs (Hammerstad et al. 1994, Burne and Lippold 1996). However, in patients with asymmetric tendon jerks the side with the more active reflexes correlated with the side with greater parkinson signs. All these abnormalities strongly contribute to postural instability in parkinsonians.

Changes in PD postural control have been mostly reported in dynamic conditions. For example, in response to toe-up or toe-down platform tilts controls usually employ an ankle strategy (a sequence of posture stabilizing movements that starts in the ankle joint) PD patients, ON-medication, use a combination of an ankle and a hip strategy (Beckley et al. 1991). In response to forward or backward support surface translations, when controls would activate the muscles on the same side of the body as the direction of the perturbation, PD patients OFF--medication will reciprocally activate muscles on both sides of the joint (Horak et al. 1992). In response to such perturbation the gastrocnemius response is followed by significantly enhanced activation of the tibialis anterior (Dakof and Mendelsohn 1986). As a result, the angular rotation at the ankle joints is slower in PD than in normal subjects due to changes in intrinsic muscle stiffness. Similarly, healthy subjects while standing on a sinusoidally oscillating treadmill maintain equilibrium mainly by activating extensor muscles (Dietz et al. 1993). In contrast, PD patients use flexor activation for this purpose and they can not maintain balance with eyes closed. The timing and amplitude of programmed adjustments are inappropriate in PD and the reduced ability to activate the leg extensors is proposed to be due to an impairment of extensor load receptor.

A great number of electrophysiological studies have concerned the function of peripheral feedback in PD (for review see Dietz et al. 1988 and Beckley et al. 1991). The most evident finding of these studies is an enlargement of amplitude and duration of the medium (M2) loop muscular response (see Rigidity section) which, as suggested earlier, (Diener et al. 1983,1984) destabilizes upright posture. This increase significantly correlates with severity of the disease. Since the muscle spindle demonstrate normal alpha-gamma coactivation in PD, an increase of reflex gain at higher CNS sites has been postulated (Burke et al. 1977). Controversy persists as to whether M2 changes are caused by cortical or spinal reflex loop gain changes (Tatton et al. 1984).

Some patients with an akinetic Parkinson syndrome of the lower extremities and a poor response to L-DOPA have been described as having 'lower body Parkinsonism' (Trenkwalder et al. 1995). These patients are characterized by poor balance control which results in frequent falls. Normally it is not possible to differentiate lower body parkinsonism from standard PD patients in either static or dynamic posturographic tests. However, when lower body parkinsonism patients are placed on foam which results in both reduced somatosensory input as well as reduced stability they are not able to compensate for induced instability (Trenkwalder et al. 1995).

AKINESIA AND BRADYKINESIA

Akinesia and bradykinesia are two major functional impairments associated with Parkinson's disease (see Delwaide and Agnoli 1985 for review). Akinesia is defined as a lack or poverty of movement. According to Narabayashi (1985), akinesia in parkinsonism can be divided into three different parts: (1) slowness and unskillfulness of movement secondary to rigidity, (2) lack or poverty of movement even after complete abolition of rigidity and absence of muscular weakness, and (3) difficulty in initiation of movement also known as "freezing". These distinctions have been made based upon responsiveness to treatment. Stereotaxic thalamotomy within the ventrolateral nucleus of the thalamus has been shown to eliminate rigidity, and the first type of akinesia.

The lack of movement, the second type of akinesia, is helped in the majority of cases by Levodopa. While "freezing", the third type of akinesia, remains one of the most debilitating aspects of PD, and can appear even after complete relief of all other symptoms of PD. Freezing has been shown to be made worse by L-Dopa but is inconsistently relieved by norepinephrine therapy (Narabayashi 1985).

Akinesia is commonly attributed to globus pallidus disfunction. However, there is evidence that akinesia may also be caused by lesions of the supplementary motor area. Patients with such lesions share the same symptoms and signs as PD patients (Caligiuri et al. 1992). The supplementary motor area represents the "central timing system". Impairment of this system results not only in movement initiation delay but also in decline of movement synchronomy.

One of the main manifestation of motor impairments in PD is a slowness of movement or bradykinesia (Draper and Johns 1964, Flowers 1976, Evarts et al. 1981, Marsden 1985, Sheridab and Flowers 1990). In many cases movement velocity correlates well with the stage of the disease (Weinrich et al. 1988). An impairment of velocity control has often been associated with apparent deficits in the ability to increase muscle activity. Some research has found that motor units are recruited at higher thresholds than normal in PD (Palmer et al. 1991), and once recruited motor units fire at lower firing rates than normal (Delwaide 1985, Palmer et al. 1991).

Flowers (1976) has made several important observations about PD bradykinesia. Short ballistic movements are accomplished with normal speed while larger movements are performed more slowly than normal. Normal subjects perform larger movements with faster velocity, thus the time of movement is kept constant. In normal subjects the execution of single rapid one-joint movements is characterized by an electromyographic pattern composed of three discrete bursts of activity; two bursts (first and second agonist bursts) are present in the agonist muscle separated by an almost complete period of electrical silence (Berardeli et al. 1996). During this pause, another burst occurs in the antagonist muscle. If a rapid movement is executed during tonic activation of the agonist muscle, tonic activity is inhibited just prior to the first agonist burst onset (agonist inhibition). Similarly, if the movement is performed during tonic activation of the antagonist muscle, such activity is also inhibited prior to first agonist burst onset (antagonist inhibition). An equivalent of the kinematic features related to the EMG pattern described above is a symmetrical and unimodal velocity profile that is bell-shaped and shows an acceleration time roughly equal to the deceleration time. This holds true for movements performed under low accuracy constraints; as accuracy demands become stricter and stricter, the peak velocity decreases but, as long as the movement is made with one continuous trajectory, the velocity profile remains roughly symmetrical. The timing and size of the bursts vary according to the speed and amplitude of the movement. The origin of the EMG pattern is a central program, but afferent inputs can modulate the voluntary activity. The basal ganglia have a role in scaling the size of first agonist burst, reinforcing the voluntary command and inhibiting inappropriate EMG activity. The cerebellum, on the other hand, seems to play a role in timing the voluntary bursts and probably in implementing muscle force phasically. In PD force generation is slower than normal (Kaneoke et al. 1989, Jordan et al. 1992a, Stelmach et al. 1992) and additionally, there are disturbed reciprocal relationships that cause isometric contractions delaying movement (Lelli et al. 1991).

The basal ganglia contribute to the planning of movements (Hallet and Khoshbin 1980). Specifically, normal people perform movements of large amplitude with faster velocity while patients with PD have been shown to keep velocity the same for all movements (Draper and Johns 1964, Flowers 1976, Hallett et al. 1977, Hallett and Khoshbin 1980, Evarts et al. 1981, Hallett 1985, Flash et al. 1992). Hallett and Khoshbin (1980) and Berardelli et al. (1986) suggested that this is so because patients with PD do not increase the amount of muscular activity occurring in the first burst of muscle contraction that starts a fast movement. In their experiments, the duration of the initial burst appeared to be normal, but its size was not adjusted with the distance requirements. Stelmach and Phillips (1991) and Jordan et al. (1992a) also found that rate of force generation in PD is slower than normal.

Many mechanisms have been proposed for why PD patients move slowly. One possible explanation is that patients with PD loose the ability to "run" motor programs without conscious effort (Barbeau 1986). Other authors state that to maintain accuracy within acceptable limits, PD patients slow their movement down to a level where they can integrate feedback to execute the movement or to flow smoothly from one motor program to the next (Barbeau 1986, Beuter et al. 1992). Most of the studies on PD have clearly shown that parkinsonians are slower to react to an external stimulus (Bloxham et al. 1984).

Marteniuk and Athenes (1985) have suggested that, for normal subjects, simple arm movements such as aiming and reaching for a target object (Fitts-like task) are functionally related to the task demands. The control and organization of hand movements, in this case, is affected by the nature and the size of a target object. Specifically, the temporal location of the peak velocity (hence, the duration of acceleration and deceleration phases) occurred both relatively and absolutely earlier when the nature of the target object required greater terminal accuracy. Sanes (1985) reported results consistent with previous studies, that is, an increase in movement amplitude or a decrease in target width resulted in slower and less accurate movements for PD subjects. However, for movements with a low index of difficulty, PD subjects were as accurate and as fast as control subjects. Such results suggest the possibility that the poorer performance of PD subjects in aiming tasks is not solely related to slow speed but might also be a result of the relative inaccuracy of movement termination. Therefore the speed deficit might not be totally accounted for by a structural deficit in the basal ganglia. The involuntary movements of PD, most notably dyskinesia and tremor, could be significant factors in poorer performance by patients rather than deficits in motor programming and information processing (Sanes 1985).

PD patients have difficulty in initiating a motor plan but no difficulty in executing the plan once it has been initiated (Bloxham et al. 1984, Marsden 1985). Further, PD subjects are thought to be capable of adapting their motor plan to new or specific environmental circumstances, as well as capable of learning a novel motor skill (Marsden 1985, Frith et al. 1986, Verschueren et al. 1997). Some attempts have been made at examining the deficits in PD subjects when two motor programs are executed simultaneously with one limb (Benecke et al. 1986), or with two limbs (Schwab et al. 1954, Cohen 1970). The results obtained in these experiments have suggested to some authors that a major deficit of PD is an inability to execute concurrent or sequential actions (Schwab et al. 1954, Margolin and Wing 1983, Marsden 1985, Benecke et al. 1986, Rafal et al. 1987, Lang et al. 1990, Caligiuri et al. 1992).

LOCOMOTION

Two types of discoordination are manifested in parkinsonian gait. One is velocity dependent and hence related to bradykinesia which was discussed in the previous section. There are also altered coordination patterns (Beuter et al. 1992). The latter abnormalities include, beside the already mentioned postural deformities, the characteristic shuffling gait with small steps and poverty of movements in the trunk and in the upper limbs (Knuttson 1972, Murray et al. 1978, Stern et al. 1983b, Forssberg et al. 1984, Nutt 1988, Kitamura et al. 1991, Weller et al. 1992, Ueno et al. 1993). During locomotion PD patients show markedly reduced ranges of angular displacements in the hip and knee joints (Knuttson and Martensson 1986). When they move flexions and extensions appear in their normal sequences within the gait cycle, though the stride cycle is longer.

In the gait of parkinsonians, most of the normal EMG activation is well preserved expect that of the hip abductors where the activation is delayed compared to the normal pattern. The observed continuous muscle activity upon normal activation observed in PD can be regarded as equivalent to rigidity (Knuttson and Martensson 1986). Recently Gantchev et al. (1996) reported that coordination between the preparatory postural adjustment of the whole body and the actual stepping movement is impaired in PD. They showed that lengthening of the postural phase was a common deficit in all forward oriented movement tasks in parkinsonian patients. This is due to the impaired production of the requisite propulsive forces providing the forward acceleration of the center of gravity. Consequently, a shortening of the first step length occurs. Although the stepping movement can be improved with the aid of sensory cues, the postural phase will always be prolonged whenever a task requiring postural adjustment is performed. Studies of the Bereitshaft--spotential preceding movement have confirmed that PD subjects, in fact, exhibit an impairment of the preparation and assembly of the complex sequences of movement necessary to initiate gait (Vidailhet et al. 1993).

Gait deficit in PD also results in lesser tolerance for changes in movement conditions. In studies in which the postural requirements were reduced by supported stance (Schieppati and Nardone 1991) or by sitting (Horak et al. 1992) PD patients showed difficulty adapting their motor programs to new conditions. Lesser tolerance to changed movement conditions was also observed in split belt treadmill locomotion (Dietz et al. 1995). While healthy subjects easily tolerated these walking conditions, parkinsonians usually reached the limits of their walking capabilities. These patients showed a restricted range of stride frequencies.

Shuffling gait is a gait with shorter steps and higher cadence. In short steps with little lifting of the foot from the floor, short regular contractions are observed in the quadriceps brachii and tibialis anterior. Their antagonists show tonic discharges or small numbers of reciprocal potentials. Additionally, reciprocity of muscular contractions between tibialis anterior and triceps surae is not clear in PD gait (Yanagisawa et al. 1991).

Two type of rhythmic activities can be distinguished in the EMG of leg muscles: one results from locomotion and the second is characterized by rapid fluctuations. In shuffling gait, the rhythm of locomotion ranges between 1.1-1.4 Hz, whereas normal subjects move with a slower cadence - below 1.1 Hz (Blin et al. 1990). In force platform recordings of the shuffle gait, the two characteristic peaks in the vertical reaction forces i.e., "weight acceptance" and "toes push off" are missing (Hughes et al. 1990, Yanagisawa et al. 1991).

Very interesting results were presented by Morris and coworkers (1994). They demonstrated that walking slows down dramatically when PD subjects were asked to performed a long gait sequence. The observed slowing of the gait was primarily due to an inability of parkinsonians to generate steps of appropriate size. Thus, it seems that the fundamental deficit in gait hypokinesia might be in the regulation of stride length. At the same time the PD subjects showed no deficit in the regulation of cadence. The authors concluded that it is possible that cadence regulation is not under basal ganglia influence whereas stride length control is mediated by the basal ganglia. They also suggest that the reduced stride in the parkinsonians might be due to inadequate preparatory processes involving the interaction between supplementary motor area and the basal ganglia.

MOTOR BLOCKS

Freezing episodes and related phenomena (as a general term, motor blocks) are poorly understood, particularly disabling, and a therapeutically frustrating problem in Parkinson's disease. Freezing and hastening phenomena are motor symptoms frequently observed in PD, even when rigidity and tremor are well controlled by L-Dopa treatment (Mestre et al. 1992).

Freezing gait is a unique gait disorder manifested by start hesitation, as if the feet were "glued" to the floor, and gait arrests, often accompanied by festination, instability, and recurrent falls (Cooke et al. 1978, Yanagisawa et al. 1991, Achiron et al. 1993, Atchison et al. 1993). Different authors used different terms to define this abnormal gait: "lower body parkinsonism", "motor blocks", "apraxia of gait", "freezing in movement".

An abrupt inability to initiate voluntary movement, especially walking, is probably the most distressing phenomenon. The state of complete immobility and helplessness may last for seconds up to, occasionally, hours when the capacity for movement abruptly returns. Attacks seem to be unrelated to the timing of individual levodopa treatment but do tend to occur when the patient is physically tired. Frequency and severity of attacks may show considerable diurnal fluctuations and are related to the duration of the disease (Stern et al. 1980). It has been suggested that the increased sensitivity to visual stimulation and to modification of the visual environment can be an important factor leading to motor blocks (Mestre et al. 1992).

Distraction of attention can also result in freezing. This is the case in psychic stress and fatigue (Yanagisawa et al. 1991). In a study of 990 PD patients (Giladi et al. 1992), one third of them had motor blocks. Longer disease duration, longer duration of L-Dopa treatment, and higher Hoehn and Yahr rating were associated with the presence of motor blocks. According to these authors the three motor tasks that are most affected by motor blocks are speech, hand writing, and gait. In gait most of the freezing episodes appear during gait initiation, turning, and while passing narrow spaces or doorways. Twenty three percent of patients had blocks on open runways. Eleven percent of parkinsonians had blocks in speech and hand writing. A total of 22% of these patients had blocks at a time when they were experiencing the maximal beneficial effect from L-Dopa.

There are many maneuvers or tricks that are used to overcome the immobility (Knuttson 1972). Luria (1932) described a patient who became completely immobile whenever he attempted to walk but who could easily run upstairs. "Frozen" patients may move when a loud verbal command is given or when an accompanying person steps forward (Lang et al. 1990). Martin (1967), in his discussion of gait and posture impairments in PD patients, mentioned a potential benefit from using parallel line cues to overcome akinetic freezing. Generally, periodic visual or auditory stimuli improve the difficulty in walking as they form a rhythm adequate to maintain repetitive movements (Richards et al. 1994). The kinematic results of elderly control subjects showed that such visual cues cause longer stride lengths without significantly altering the stride duration or cadence. Auditory

cues on the other hand induce a faster cadence and a longer stride length. The results in the PD patients (OFF L-Dopa) showed that visual cues induce a longer stride length and a longer stride duration. Auditory cues caused shorter stride duration and a longer stride length. Richards et al. (1994) concluded that visual cues may exert their effect on spatial elements of movement (e.g., limb movement amplitude) and auditory cues act more on centrally controlled variables such as stride length and cadence. This also suggests that the motor program in PD is preserved and the problem is to access it or transform it into an action.

Motor blocks can be observed in the execution of many different motor programs involving different body segments. Narabayashi and Nakamura (1985) studied finger tapping in 123 parkinsonians. Seventy-two percent of their subjects could not make 50 to 100 taps above 2.5 Hz. The authors related the festination they observed to disturbances in rhythm formation due to norepinephrine deficiency in the central nervous system (Narabayashi and Nakamura 1985).

SENSORY SYMPTOMS

Although sensory symptoms were not originally described in Parkinson's disease, in recent years it has been increasingly recognized that painful sensations and paresthesias occur in approximately 40% of patients (Shulman et al. 1996). PD patients often describe a sensation of internal tremor, a feeling of tremor inside the chest, abdomen, arms, or legs that cannot be seen. The frequency of other sensory symptoms (aching, tingling, burning) was higher in the PD patients with internal tremor (73%) than in those without (45%). Internal tremor is associated with anxiety which can also affect motor performance.

CONCLUDING REMARKS

Significant progress in the understanding of PD symptoms has been made in the recent years. However, many unresolved problems still remain. For example movement impairments as observed in parkinsonism could be also due to perceptual, predictive, executional, or motor sequencing deficits (Cassel et al. 1973, Cooke et al. 1978, Sharpe et al. 1983, Stern et al. 1983b, Bloxham et al. 1984). Hence it has been difficult to infer, without ambiguity, either the specific process(es) involved in an impairment, or its pathophysiological correlates. Therefore, it is naive to suggest that motor deficits associated with PD subjects are localized purely in the basal ganglia. The basal ganglia mediate between higher and lower brain structures, receiving, for example, inputs from cortical areas and the substantia nigra, and innervating thalamic and midbrain nuclei (DeLong et al. 1983, Tatton et al. 1984). Given these interconnections and the distributed nature of the neural processes, consideration must be given to the inputs the basal ganglia relay, how they process these inputs, and what structures are modulated by their outputs. Thus it is necessary to consider the neural flow of activity during movement production from cortex, to basal ganglia and down to muscles. Does each structure deal with its inputs adequately, and how long does it require to do so? Any consideration of structural impairment requires an assessment of motor functioning, and so the functional correlates of movement production should be documented. Cognitive neuroscience faces the task of supplementing the neurophysiological data base with detailed descriptions of how and when a structural deficit is causing an impairment of function.

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DRUG THERAPY

New Directions in the Drug Treatment of Parkinson's Disease

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Contents

Summary

Parkinson's disease, a clinical syndrome with 4 cardinal features (bradykinesia, resting tremor, increased muscular rigidity and impaired postural balance), is mainly caused by the loss of dopaminergic neurons in the substantia nigra pars compacta. Although levodopa remains the 'gold standard' in the treatment of the disease, several emerging strategies are currently being developed. The first concerns new symptomatic drugs that either potentiate the effects of levodopa (e.g. slow-release preparations of levodopa, catechol-*O*-methyltransferase inhibitors and new dopamine agonists) or target clinical symptoms resistant to dopaminergic drugs (e.g. glutamate antagonists). The second strategy is to find drugs that are able to prevent or delay the neuronal death observed in Parkinson's disease. Several neuroprotective drugs are now in development in experimental research, but clinical trials in this area are still lacking. The development of these new drugs also depends on the validation of new clinical methodologies.

Parkinson's disease (PD), one of the commonest causes of disability among the elderly, is usually defined as a clinical syndrome with 4 cardinal features: bradykinesia (slowness and poverty of movement); resting tremor; rigidity; and abnormalities of posture and gait. Since the discovery of the beneficial effects of levodopa 35 years ago, few areas in pharmacology and medicine have surpassed PD in terms of progress in our understanding of the mechanisms involved and in drug treatment. Major advances in the pharmacological treatment of PD, and especially the introduction of levodopa, have markedly reduced morbidity and are an example of the triumph of rational pharmacology. This article reviews some recent aspects of PD, including advances in drug research and a discussion of future strategies for the treatment of this disease.

Table I. UK Parkinson's Disease Society Brain Bank clinical diagnostic criteria (from Gibb & Lees,[9] with permission)

Step 1. Diagnosis of parkinsonian syndrome
Bradykinesia (slowness of initiation of voluntary movement with progressive reduction in speed and amplitude of repetitive actions)
And at least 1 of the following:
muscular rigidity
4-6Hz resting tremor
postural instability not caused by primary visual, vestibular, cerebellar or proprioceptive dysfunction
Step 2. Exclusion criteria for Parkinson's disease
History of repeated strokes with stepwise progression of parkinsonian features
History of definite encephalitis
Oculogyric crises
Neuroleptic treatment at onset of symptoms
More than 1 affected relative
Sustained remission
Strictly unilateral features after 3 years
Supranuclear gaze palsy
Cerebellar signs
Early severe autonomic involvement
Early severe dementia with disturbances of memory, language and praxis
Babinski sign
Presence of cerebral tumour or communicating hydrocephalus on CT scan
Negative response to large doses of levodopa (if malabsorption excluded)
MPTP exposure
Step 3. Supportive prospective positive criteria for Parkinson's disease[a]
Unilateral onset
Resting tremor present
Progressive disorder
Persistent asymmetry affecting the side of onset most excellent response (70-100%) to levodopa
Severe levodopa-induced chorea
Levodopa response for 5 years or more
Clinical course of 10 years or more

a Three or more are required for a definite diagnosis of Parkinson's disease.

Abbreviations: CT = computerised tomography; MPTP = methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

1. Pathophysiology

The main hallmark of PD is the loss of dopaminergic neuron cell bodies in the zona compacta of the substantia nigra, leading to striatal dopamine denervation.[1,2] The dopaminergic defect explains the main clinical manifestations of PD (especially akinesia, rigidity and, to a lesser extent, tremor), although symptoms emerge only when such depletion exceeds 80 or 90%.

In addition to nigrostriatal dopamine denervation, postmortem studies have documented other biochemical abnormalities in the brains of patients with PD. These include mesocorticolimbic dopamine cell loss and decreases in hypothalamic dopamine levels. Changes in non-dopaminergic systems, such as reduced levels of several monoamines and peptides in the striatum, substantia nigra, globus pallidus, nucleus accumbens, limbic and/or cortical regions, hippocampus, cerebellar cortex and spinal cord, may also be responsible for some of the clinical characteristics of PD.[2,3] For example, the decrease in serotonin (5-hydroxytryptamine; 5-HT) and noradrenaline (norepinephrine) levels could explain the occurrence of depressive symptoms. It has also been proposed that the noradrenergic defect may explain the 'freezing' phenomena that occur during walking.

The cell loss observed in the intermediolateral cell column, the hypothalamus and the nucleus vagus dorsalis may be involved in the autonomic dysfunction observed in some patients with PD.[2,3] Peripheral autonomic changes, including hyposensitivity of α_2 adrenoceptors and hypersensitivity of peripheral vascular dopaminergic receptors with normal α_1 or β adrenoceptor sensitivity, have also been described.[4] However, the clinical consequences of all these central and peripheral changes remain unclear.

Recent knowledge about the interconnecting neuronal circuitries within the basal ganglia and the cellular compensatory effects of dopamine loss has focused interest on amino acids, and in particular glutamate, which is an excitatory neurotransmitter in the basal ganglia. A growing body of evidence suggests that striatal dopaminergic denervation results in overactivity of both the subthalamic nucleus and ventroanterior and ventrolateral nuclei of the thalamus, leading to reduced inhibitory input to the

Table II. Classification of parkinsonism (from Jankovic,[7] with permission)

- Primary Parkinson's diseases
- Idiopathic
  - tremor
  - postural instability and gait difficulty
  - akinesia ('freezing')
  - dementia
  - depression
  - sensory disturbance
  - autonomic dysfunction
- Brain tumour
- Trauma and psychistic encephalopathy
- Hydrocephalus (normal and high pressure)
- Syringomesencephalia
- Multiple system atrophies
- Sporadic
  - progressive supranuclear palsy (ophthalmoparesis)
  - Shy-Drager syndrome (dysautonomia)
  - olivopontocerebellar atrophy (ataxia)
  - Parkinsonism-dementia-ALS complex (motor neuron disease)
  - striatonigral degeneration
  - corticodentatonigral degeneration with neuronal achromasia
  - Alzheimer's disease
- Inherited
  - Huntington's disease
  - Wilson's disease
  - Hallervorden-Spatz disease
  - familial parkinsonism–dementia syndrome
  - familial basal ganglia calcification
  - neuroacanthocytosis
  - spinocerebellar-nigral degeneration and Joseph's disease
  - GDH deficiency

Abbreviations: ALS = amyotrophic lateral sclerosis; GDH = glutamate dehydrogenase.

cortex. Glutamate is believed to be the major neurotransmitter between the subthalamic nucleus and the substantia nigra, and between the substantia nigra and the thalamus.[5]

2. Diagnosis

Before considering recent advances in the pharmacology of PD, it is important to discuss the problems associated with its diagnosis. A review of the differential diagnosis of PD is beyond the scope of this article. However, in clinical practice, one of the first questions concerns the idiopathic nature of the disease and its response to levodopa. In fact, although the clinical features of PD are well known, there are at present no universally accepted pathognomonic diagnostic criteria. Indeed, as in Alzheimer's disease and other dementias, the diagnosis of idiopathic PD can be made only at post-mortem, with the detection of Lewy bodies. Brain-bank studies have identified some criteria that are helpful in the diagnosis of PD (table I).[6]

Symptoms of PD can also be associated with several other clinical conditions, for example dementia, depression, autonomic dysfunction and cerebellar disorders. Thus, classifications of parkinsonism usually differentiate between primary (idiopathic) PD, secondary parkinsonism and multiple system atrophy (MSA) [table II].[7,8] This review focuses only on recent advances in idiopathic PD.

3. Emerging New Strategies and New Drugs

The discovery of dopamine terminal loss in the striatum and the observation that the striatal cholinergic terminals remain fully active have led to the current pharmacological approach to treating PD. Treatment is aimed at restoring the disturbed neurotransmitter balance, either by: (i) inhibiting acetylcholine output with antimuscarinic drugs; or (ii) countering the dopamine deficiency through supplementation with levodopa and/or dopamine agonists. Recent pathophysiological studies have also allowed researchers to characterise some cellular mechanisms of neuronal death in the substantia nigra. Thus, interest in new therapeutic strategies includes research not only for new drugs but also for effective preventive strategies.

3.1 Symptomatic Treatment

In most patients with PD, the initial therapeutic success of levodopa is blunted by the development of motor and mental adverse effects after a few years of treatment.[4] Because of the limitations of levodopa therapy, the pharmacological treatment

of PD has been expanded to incorporate 4 different approaches:

- the development of new dopaminergic drugs, or the reassessment of old drugs in new strategies or delivery systems, to lessen the long-term adverse effects of levodopa;
- research for agents that target non-dopaminergic neurotransmitter systems;
- studies of the feasibility of brain transplants;
- new surgical approaches.

Only the first 2 areas are discussed in this article.

3.1.1 Enhancing Dopaminergic Transmission

Several clinical pharmacological studies have suggested that motor response complications are a consequence of both natural disease progression and the action of levodopa. It has been suggested that wearing-off responses appear to be primarily related to advancing degenerative changes affecting the dopaminergic nerve endings. Other fluctuations (e.g. peak-dose dyskinesias, or 'on-off' effects) could be explained by the chronic intermittent excitation (by levodopa treatment) of postsynaptic dopamine receptors, which are normally tonically stimulated.[9] Thus, strategies that improve dopaminergic neurotransmission could be useful to prevent or treat complications such as wearing-off responses.

Levodopa

Despite its long-term adverse effects, levodopa remains the 'gold standard' in PD patients. It is rapidly absorbed in the duodenum and transported across the gut wall by a saturable, facilitated carrier system (the aromatic and branched chain L-amino acid system).[10] Peak concentrations of the drug in plasma occur between 0.5 and 2 hours after an oral dose; there are, however, large inter- and intraindividual variations depending, for example, on the rate of gastric emptying and gastric pH.

Levodopa is always administered in combination with a peripherally acting dopa decarboxylase inhibitor (benserazide or carbidopa). This reduces some of the peripheral adverse effects of levodopa (cardiac arrhythmias, nausea, vomiting, etc.) and increases the fraction of administered levodopa that crosses the blood-brain barrier.

Because of rapid decarboxylation and the blood-brain barrier, less than 1% of the administered levodopa penetrates into the brain, even in the presence of a peripheral dopa decarboxylase inhibitor. Amino acids in the diet can compete with levodopa transport across both the intestinal mucosa and the blood-brain barrier. This observation led to the proposal to use low-protein diets in patients with levodopa-induced fluctuations in motor performance. Although the results of the studies are controversial, most of them show that this regimen increases the ratio of 'on' to 'off' hours.[11,12] Benefit usually occurs within a week of diet initiation.[11] The authors recommend that patients take levodopa with a carbohydrate-containing breakfast and lunch, and consume more protein with the evening meal.[12] This kind of regimen can be useful for some patients. However, since it often reduces protein intake, it could lead to malnutrition in elderly parkinsonian patients.

Another option is the use of slow-release preparations of levodopa (e.g. 'Sinemet CR', 'Madopar HBS'). 'Sinemet CR' is a mixture of levodopa 200mg and carbidopa 50mg in an erodible matrix that retards gastric tablet dissolution.[13] 'Madopar HBS' is a controlled-release tablet with levodopa 100mg and benserazide 25mg. When in contact with gastric fluid and after dissolution of the gelatin shell of the capsule, the 'hydrodynamically balanced system' (HBS) forms a mucous body with a bulk density of less than 1. This releases the drug at the desired rate while the dosage form remains in the stomach for a prolonged period of time.[14]

However, it is important to consider that 'Sinemet CR' and 'Madopar HBS' are not true extended-release dosage forms, but are formulations that produce attenuated peak plasma drug concentrations (C_{max}) and release the active compound slowly (i.e. they have reduced bioavailability). This indicates that the total daily dosage of levodopa may need to be increased by about 30% when switching from standard to slow-release levodopa.

Several studies have shown that 'Sinemet CR'[15,16] or 'Madopar HBS'[17,18] are effective drugs that prolong 'on' time, especially in patients with

wearing-off responses. Disadvantages of these slow-release preparations include delayed and poor responses after the first morning dose (it is often necessary to take a standard tablet as the first daily dose) as well as an exacerbation and prolongation of peak-dose dyskinesias (especially in the afternoon). The place of 'Sinemet CR' or 'Madopar HBS' as first-line treatment of PD in patients not previously treated with standard levodopa is not established.[19] Studies are now under way to investigate whether the more constant activation of dopaminergic neurons achieved by slow-release compared with standard levodopa could prevent or delay the occurrence of motor fluctuations.

Other researchers have sought to improve the delivery of levodopa to the gastrointestinal system or brain using intraduodenal, intravenous or intracerebroventricular infusion, or percutaneous administration.[20] Another exciting area of future research is the development of encapsulated dopamine-secreting cell lines, which could be implanted subcutaneously or into the striatum.[21]

Increasing Dopamine Synthesis

Clinical trials of dopamine precursors (e.g. tyrosine) or agents that stimulate tyrosine hydroxylase (tetrahydrobiopterin, oxyferriscorbone) have failed to give reproducible and significant results.

Enhancing Dopamine Release

Amphetamines are known to increase dopamine release from nigrostriatal terminals. However, these drugs, which have several adverse effects (hypertensive crisis, depression, dependence, etc.), have not been found to be useful in parkinsonian patients.[22]

Amantadine, first introduced as an antiviral agent for the prophylaxis of influenza, is a unique antiparkinsonian drug with multiple mechanisms of action: it enhances dopamine release and has anti-muscarinic effects, but it may also increase dopamine synthesis and inhibit dopamine reuptake.[23] Recent studies also suggest that amantadine and the closely related compound memantine can block *N*-methyl-D-aspartate (NMDA) receptors.[24] Whatever its exact mechanism of action, the effects of amantadine on bradykinesia and tremor are modest and the drug is less effective than levodopa. Most patients fail to respond after several (3 to 6) months of treatment. However, amantadine is one of the only antiparkinsonian drugs possessing lateral psychostimulant properties, which can be useful in some patients.

Several authors have reported favourable results with electroconvulsive therapy (ECT) in patients with PD (for a bibliography, see Atre-Vaidya & Lampala[25]). ECT may improve motor as well as depressive symptoms.[25] However, most studies have so far been small and uncontrolled. Further study in this area is therefore needed.

Blocking Dopamine Reuptake

Blocking dopamine reuptake is known to increase dopamine levels in the synapse. However, drugs such as imipramine derivatives, amfebutamone (bupropion), mazindol and benzatropine (benztropine), which are known to block dopamine reuptake, have only a modest effect on motor symptoms in patients with PD.

Inhibiting Dopamine Metabolism

Most of a dose of orally administered levodopa is rapidly metabolised, first by peripheral dopa decarboxylase to dopamine (about 70%), which is further metabolised by intracellular monoamine oxidase (MAO) and extracellular catechol-*O*-methyltransferase (COMT).[10] The latter is present both peripherally and in the brain.

MAO is an enzyme that catalyses the oxidative deamination of various neurotransmitters such as catecholamines and serotonin. It exists in 2 forms. The B form, mainly located in platelets and the striatum, is responsible for the degradation of dopamine and other phenylethylamines, whereas the A form degrades serotonin. At low to moderate dosages (≤10 mg/day), selegiline (deprenyl) is a selective inhibitor of MAO-B and is free of the 'tyramine effect' common to other MAO inhibitors. It acts as an irreversible 'suicide' inhibitor of the enzyme. Its mechanisms of action have recently been reviewed.[26,27]

Selegiline has been used for many years as an adjunct to levodopa therapy, although its symptomatic benefit is relatively modest. It has been shown

to attenuate drug-induced motor fluctuations such as wearing-off effects in 50 to 70% of patients, and permits a 10 to 30% reduction in the total daily dosage of levodopa. In some patients, selegiline exacerbates peak-dose adverse effects of levodopa (e.g. dyskinesias, dystonia, confusion and hallucinations). Patients with severe, unpredictable on-off effects do not usually respond to selegiline. Used as monotherapy, this drug appears to be ineffective in some patients previously untreated with levodopa and effective in some other patients.[26] The putative neuroprotective effects of selegiline are discussed in section 3.3.

A recently published trial of selegiline has questioned the safety of the drug in PD.[28] A prospective study designed to compare the effectiveness of levodopa, bromocriptine and levodopa plus selegiline in early mild PD found a significantly higher mortality rate in the group of patients treated with selegiline plus levodopa compared with levodopa alone.[28] Until more information becomes available from this study, this surprising result must be interpreted cautiously, since several methodological biases could exist (number of lost patients, cause of death, risk α, etc.).[29]

Another potential source of bias in this study could be interactions between selegiline and antidepressants that inhibit serotonin reuptake. This would lead to so-called 'serotonin syndrome', characterised by anxiety, loss of consciousness, seizures or even pseudophaeochromocytoma crisis.[30] This interaction is well recognised with older serotonin reuptake inhibitors (e.g. fluoxetine) that are metabolised by cytochrome P450. Further studies are needed to investigate this interaction with newer serotonin reuptake inhibitors (e.g. citalopram).

Several other MAO inhibitors derived from amphetamine-like metabolites are currently in development as future antiparkinsonian drugs (e.g. lazabemide).[31] The development of mofegiline[32] has been stopped.

A series of new and selective COMT inhibitors has recently been developed. Entacapone, nitecapone and tolcapone are nitrocatechol-type agents active both *in vitro* and *in vivo*, whereas CGP28014 is a pyridine derivative that is active only *in vivo*.[33] The main action of these agents is to inhibit the *O*-methylation of levodopa, thus improving its bioavailability and brain penetration, and potentiating its motor effects.[34] Entacapone and nitecapone have mainly peripheral effects, whereas tolcapone and CGP 28014 are also active in the brain.

Several recent clinical studies have shown that COMT inhibitors reduce plasma levels of 3-*O*-methyldopa, which is believed to compete with levodopa transport through the intestinal mucosa as well as through the blood-brain barrier. COMT inhibitors do not affect levodopa absorption (i.e. the maximum plasma concentration is unchanged), but they do prolong its half-life. This increases the duration of action of a single dose of levodopa, and for this reason COMT inhibitors may be useful as adjunctive therapy in PD.[35,36] COMT inhibitors may also facilitate a reduction in the dosage of levodopa.

Future studies must investigate the long-term beneficial and adverse effects of COMT inhibitors. For example, COMT inhibitors may worsen dyskinesias. In that case, the dosage of levodopa should be reduced or the dosage interval prolonged.

Continuous Dopamine Therapy

Two factors have led to the proposal that continuous treatment of PD could delay the onset of treatment complications. The first of these is the hypothesis that peak-dose dyskinesias and on-off effects can be explained by intermittent stimulation of the postsynaptic dopamine receptors.[9,37] Secondly, it has been observed that more constant activation of dopamine receptors, through continuous infusion of levodopa or dopamine agonists (which causes fewer receptor alterations than pulsatile dopaminergic stimulation), counteracts some motor fluctuations in patients with advanced PD.[36] Continuous dopaminergic stimulation could be achieved by a long-term infusion of levodopa or apomorphine (a dopamine agonist) in previously untreated PD patients. Of course, for evident reasons, such a possibility cannot be investigated in humans.

The goal of continuous dopamine stimulation could justify, from a theoretical point of view, the use of slow-release levodopa formulations as first-line treatment of the disease. As indicated above, the place of these formulations in previously untreated patients remains unknown, and the results of a large, multicentre, controlled trial comparing standard and slow-release levodopa in this patient group are awaited with interest. Another possibility could be long-acting dopaminomimetic drugs (dopamine agonists), which may offer a more physiological pattern of stimulation.

Dopamine Agonists

Because the efficacy of levodopa wanes over time in many PD patients, interest has turned to the development of drugs acting directly on dopamine receptors. Dopamine agonists include ergot derivatives, apomorphine and more recently developed drugs.

Ergot Derivatives

The current status of dopamine agonists in PD was recently reviewed.[38] Dopamine agonists are a heterogeneous group of drugs that produce their antiparkinsonian effect through the activation of dopamine receptors. They were first developed in the early 1970s and, to date, bromocriptine, lisuride and pergolide have undergone extensive clinical trials and are now used in clinical practice. These drugs are ergot derivatives. Dopamine agonists act directly on postsynaptic dopamine D_1 and/or D_2 receptors. The primary target of dopamine agonists is believed to be the D_2 receptor, although some recent studies have suggested a role for D_1 receptors in the treatment of PD.[39]

The binding profiles of dopamine agonists at D_1 and D_2 receptors differ slightly. Bromocriptine stimulates only D_2 receptors and is a partial agonist at D_1 receptors. Lisuride is a potent D_2 and a weak D_1 receptor agonist. Pergolide stimulates D_2 more than D_1 receptors.[38] Despite their different pharmacodynamic and pharmacokinetic profiles, the 3 drugs appear to be very similar in terms of their clinical efficacy.

This pharmacological profile suggests certain theoretical advantages of these drugs over levodopa: (i) they stimulate postsynaptic dopamine receptors directly, thus bypassing the degenerating nigrostriatal neurons; (ii) they do not depend on a pool of decarboxylase enzyme for conversion into the active transmitter; (iii) in contrast to levodopa, which yields 6-hydroxydopamine, they do not produce toxic metabolites; and (iv) their use will not result in the formation of free radicals, which have potential adverse consequences on disease progression. Moreover, their use permits reduction of the levodopa dosage.[38]

Dopamine agonists also have some clear disadvantages over levodopa: (i) they are less effective in reducing parkinsonian symptoms; (ii) they produce adverse effects (orthostatic hypotension, vasoconstriction, limb oedema, retroperitoneal fibrosis, psychiatric disorders); and (iii) they are more expensive.[38]

Dopamine agonists are usually used in combination with levodopa when late adverse effects occur, especially wearing-off effects, or when the efficacy of levodopa wanes.[38] They can also be prescribed as monotherapy in some patients, and relatively high dosages can be used as initial treatment. However, their efficacy often decreases after 1 to 3 years.[40] Another possibility is combination therapy, which is known to delay the onset of levodopa-induced late adverse effects (abnormal movements, fluctuations in daily motor performance).[41,42] At present, the best therapeutic strategy (i.e. early[41][1] *vs* late[42][2] combination with levodopa), and the place of these drugs compared with others such as selegiline, remains unknown.

Apomorphine

The rediscovery of apomorphine for the management of patients with PD is one of the best examples of the value of 'old drugs' in modern pharmacology. Apomorphine is the most potent dopamine agonist now available, acting at both D_1

1 Early combination treatment refers to initial treatment with a dopamine agonist plus levodopa.
2 Late combination treatment means initiating therapy with a dopamine agonist and adding in levodopa later on, reverting to dopamine agonist monotherapy when the efficacy of dopamine replacement declines.

and D_2 receptors.[43] Its long-term oral use has been associated with nausea, vomiting and azotaemia, and is limited by hepatic first-pass metabolism. In combination with domperidone, the subcutaneous administration of apomorphine produces a potent and rapid antiparkinsonian action. Apomorphine alleviates bradykinesia and rigidity as well as parkinsonian tremor.

Repeated subcutaneous injections of apomorphine (using a 'Penject' system) significantly reduce daily 'off' periods in patients with fluctuating motor function. Benefits occur within 5 to 15 minutes and last for 45 to 90 minutes. Apomorphine has relatively few adverse effects, and adverse psychiatric reactions seem to be less frequent than with other dopamine agonists. Markedly disabled patients with frequent fluctuations (>10 per day) can be managed with continuous daytime subcutaneous infusions of apomorphine via a syringe driver.[43]

Apomorphine can also be used as a test for dopaminergic responsiveness. This test has a good predictive value for subsequent responsiveness to levodopa treatment, and may help in the differential diagnosis of idiopathic PD and parkinsonian syndromes.[43]

Current research is ongoing into alternative routes of administration for apomorphine. It is effective by the sublingual route, but the time to its onset of action is longer than after subcutaneous injection.[43] Apomorphine has also been found to be effective after rectal or intranasal administration for treating 'off' periods.[43] Although the long-term adverse effects of apomorphine are unknown, these routes could be useful in patients unable to administer apomorphine by subcutaneous injection.[43]

New Dopamine Agonists

Several other dopamine agonists are currently under development,[44,45] including cabergoline [an ergoline derivative with a long half-life (24 hours)], and the non-ergot derivative ropinirole, which is a potent D_2 receptor agonist.[46] Pramipexole is a D_2 autoreceptor agonist that is under clinical development. In addition, the possible usefulness of dopamine partial agonists, such as terguride, is currently under investigation. Other selective D_1 and D_2 receptor agonists and transdermal preparations are also being studied.[44,45]

The development of dopamine agonists was a major step forward in the treatment of PD, but the ideal drug (i.e. orally active, long-acting and as potent as levodopa) has not yet arrived. Such an ideal drug should induce fewer motor complications than levodopa, have no psychiatric adverse effects, and could be used alone to specifically stimulate central dopamine receptors.[38]

It will be necessary to reassess the pharmacological profile of existing and future dopamine agonists in accordance with the new molecular classification of the 5 known dopamine receptor subtypes.[47] At present, the roles of the different receptor subtypes remains unknown, although in primates the D_3 receptor is present in significant numbers in the caudate-putamen. Both D_1 and D_2 receptor agonists induce dyskinesias in drug-naive or levodopa-treated animals. Recent experimental studies suggest that low dosages of D_1 receptor agonists might have antiparkinsonian effects without inducing dyskinesias. On repeated administration, such treatment diminished the intensity of dyskinesias in levodopa-primed, methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP)–treated primates.[39,48]

In previously untreated patients with PD, D_1 receptor agonists exert a mild antiparkinsonian effect, mainly reducing tremor.[49] It has been suggested that a strategy which includes D_1 receptor activation and reduces the sensitivity of the D_2 receptor could provide good symptomatic control and reduce dyskinesias in patients with advanced PD.[37] Clinical studies are needed to confirm this, however.

3.1.2 Manipulating Non-Dopaminergic Neurotransmitters

As discussed in section 1, several significant biochemical changes in non-dopaminergic systems have been described in patients with PD. Thus, many workers have tried to manipulate neurotransmitters other than dopamine and acetylcholine

to find evidence for an adjuvant effect of levodopa or effects on parkinsonian symptoms that do not respond well to levodopa (e.g. gait disorders (freezing), postural instability, dysarthria, cognitive disorders).

Cognitive disorders in parkinsonian patients probably result from multiple alterations in neurotransmitter systems, involving for example noradrenaline, acetylcholine or even peptide transmitters. The manipulation of these neurotransmitters has not resulted in any observable improvement of cognition in patients with PD. In contrast, the serotonin precursor 5-hydroxytryptophan (5-HTP) and serotonin reuptake inhibitors (e.g. fluoxetine) have been shown to provide a mild antidepressant effect in patients with PD.[50] The favourable effect of progabide, a γ-aminobutyric acid agonist, suggested by Bartholini et al.[51] has not been confirmed by others.[51] Naltrexone, an opiate antagonist, was found to be ineffective in PD in patients with and without dyskinesias.[52]

More interesting is the discussion of the clinical correlation between central noradrenergic depletion and PD. This could explain the occurrence of depression, dementia, motor blocks (freezing) and orthostatic hypotension in patients with PD. For example, Japanese authors have reported that droxidopa (dihydroxyphenylserine; L-threo-dops) can improve freezing phenomena,[53] although this beneficial effect was not confirmed by others. Since droxidopa is an immediate precursor of noradrenaline, it may improve the orthostatic hypotension often observed in patients with PD.[54]

It was recently suggested that noradrenaline may play a neuroprotective role in PD,[55] since lesions of the locus coeruleus by 6-hydroxydopamine in MPTP-treated monkeys are associated with a more marked dopamine depletion and greater substantia nigra cell loss compared with nonlesioned controls.[56] The locus coeruleus may have a protective effect on nigral dopaminergic neurons. Since it is known that α_2 adrenoceptors inhibit the release of dopamine from the caudate nucleus,[57] it could be suggested that α_2 adrenoceptor antagonists could exert beneficial (neuroprotective and/or symptomatic) effects in PD. Preliminary studies are encouraging[58] but unequivocal evidence is still awaited.

Recent physiological studies have demonstrated the importance of excitatory amino acids, particularly glutamate, in the basal ganglia. For example, the excessive output from the subthalamic nucleus to the internal pallidal segment, and to the reticular part of the substantia nigra, that occurs in PD is mediated by glutamate.[5] Animal studies have shown that NMDA receptor antagonists potentiate the effects of levodopa and can protect the substantia nigra from MPTP-induced neurotoxicity in rats. Injection of the NMDA receptor antagonist dizocilpine (MK 801) within the medial pallidum reverses parkinsonian symptoms in MPTP-treated monkeys.[59]

The mechanism of action remains unclear, but it has been suggested that blockade of NMDA receptors facilitates dopamine action by preventing the glutamate-induced dephosphorylation of DARPP-32, a dopamine- and cyclic adenosine monophosphate (cAMP)–regulated phosphoprotein.[59] Despite some experimental evidence, clinical data are still lacking because the few clinical studies that have been conducted with NMDA receptor antagonists have failed to demonstrate any favourable effect in patients with PD.[60,61] Further studies with new drugs are needed.

A frequently observed long-term complication of treatment with levodopa in patients with advanced PD is the occurrence of mental disturbances – hallucinations, vivid dreams, paranoid ideation and delirium. These psychiatric symptoms reflect the consequences of dopaminergic stimulation on an underlying degenerative neuropathological process. They can be improved by reducing the levodopa (and/or dopamine agonist) dosage or by adding antipsychotics, although these invariably worsen the parkinsonian symptoms.

Clozapine is an atypical antipsychotic developed more than 30 years ago, which was withdrawn from clinical use because of its ability to cause bone marrow suppression. It is now under reinvestigation in the management of psychosis

refractory to standard treatment. In contrast to other antipsychotics, clozapine acts as a relatively selective D_1 antagonist. It also blocks the D_4 receptor in the limbic system and possesses potent antimuscarinic activity, which may explain the low incidence of extrapyramidal adverse effects associated with its use.

Consequently, several authors have investigated the use of clozapine in patients with PD and psychotic symptoms.[62,63] The results were reported to be favourable, although the studies were performed with a large range of dosages (6.5 to 250 mg/daily) on a relatively small number of patients without double-blinding.[62,63] Despite several adverse effects (hypotension, tachycardia, sialorrhoea and, more importantly, granulocytopenia (which occurs in 1 to 5% of patients during treatment)), clozapine represents an important therapeutic advance in some PD patients with mental disorders after long-term levodopa treatment.

3.2 Neuroprotective Strategies

The precise mechanism of neuronal death in PD remains unknown. Several factors are involved, including oxidative stress, mitochondrial abnormalities, calcium cytotoxicity, iron accumulation, excitotoxic or immunological factors.[64,65] These biochemical observations have resulted in new therapeutic strategies aimed at preventing the natural progression of the disease.[65]

3.2.1 Antioxidative Properties of Selegiline

The discovery that selegiline can prevent the neurotoxic effects of MPTP in animals led to the reassessment of selegiline in previously untreated patients with PD. It was speculated that selegiline might alter the progression of the disease by reducing the generation of potentially neurotoxic substances from either endogenous or exogenous compounds.

Birkmayer et al.[66] found that patients treated with selegiline plus levodopa survived 12% longer than those treated with levodopa alone. However, this was a retrospective, uncontrolled study that had major methodological defects. Tetrud and Langston[67] reported the results of a double-blind, placebo-controlled trial of selegiline in 54 patients with early PD who had never received levodopa. Patients treated with selegiline for 3 years were able to do without levodopa for 549 days, compared with 312 days for those receiving placebo. The rates of progression of 4 clinical rating scales were slowed by between 40 and 64%.

The most interesting results come from the DATATOP study.[68] This study compared the effects of placebo and selegiline on the progression of disability in early PD. An interim analysis revealed that the rate of reaching the end-point (i.e. adding levodopa) was much slower in the selegiline-treated group than in the placebo group. The final report showed that the beneficial effects of selegiline, which occurred largely during the first 12 months of treatment, remained strong and significantly delayed the onset of disability requiring levodopa therapy. The between-group difference in the estimated median time to the end-point was about 9 months. The ratings for PD improved during the first 3 months of selegiline treatment, and the motor performance of selegiline-treated patients worsened after treatment was withdrawn.[68] The authors concluded that selegiline 10 mg/day delays the onset of disability associated with early, otherwise untreated, PD.

This study raises a number of methodological, clinical and pharmacological questions. From a methodological point of view, the criteria selected (probability of reaching the end-point and ceasing full-time employment) have not been validated by previous studies. The clinical significance of the study also remains debatable because the long-term (5 to 10 years) consequences remain unknown. Finally, the mechanism of action (antidepressant, symptomatic, protective or all of these) of selegiline is unclear[69] (table III).

Two clinical trials have recently reinvestigated the neuroprotective effects of selegiline in PD.[70,71] The SINDEPAR trial[70] (performed on 86 previously untreated patients) is comparing 4 treatments in PD patients: (i) selegiline plus levodopa; (ii) selegiline plus bromocriptine; (iii) placebo plus levodopa; and (iv) placebo plus bromocriptine.

Table III. Possible mechanisms of action of selegiline (from Jankovic,[69] with permission)

Enhancement of dopaminergic transmission
Inhibits oxidation of MPTP to MPP+
Produces amphetamine-like effect
enhances release of dopamine
blocks reuptake of dopamine
Increases striatal phenylethylamine levels
enhances release of dopamine
activates dopamine receptors
Stimulates gene expression of L-amino acid decarboxylase in PC12 cells
Neuronal protection
Reduces production of oxidative radicals
Up-regulates superoxide dismutase and catalase
Suppresses nonenzymatic, iron-catalysed auto-oxidation of dopamine and polymerisation of dopamine-melanin
Neuronal rescue
Compensates for loss of target-derived trophic support (stereospecific)
Enhances glial activation
Induces NT-3/trkC receptor
Up-regulates CNF gene expression in astroglial cell culture
Delays apoptosis in serum-deprived PC12 cells
Blocks apoptosis-related fall in mitochondrial membrane potential

Abbreviations: CNF = ciliary neurotrophic factor; MPP+ = active metabolite of MPTP; MPTP = methyl-4-phenyl-1,2,3,6-tetrahydropyridine.

This study included a 7-week wash-out period of selegiline to exclude a symptomatic effect. Motor deterioration was more pronounced in the 2 placebo groups, suggesting that selegiline can delay the progression of signs and symptoms via a mechanism that is not readily accounted for by its symptomatic effects.[70]

The second trial[71] is a long-term, controlled study being performed in Finland, comparing the need for levodopa in previously untreated patients given placebo or selegiline for 4 years. It showed that the levodopa dosage was 58% higher in the placebo group than in the selegiline group, with a lower daily levodopa intake and end-of-dose deterioration in the latter.[71]

This study needs to be completed, and further trials are required to better define the respective roles of selegiline and other drugs (e.g. dopamine agonists) that can be used as first-line treatment in the early management of PD.

Other studies have failed to find evidence for a neuroprotective effect of selegiline. For example, Brannan and Yahr[72] compared 2 groups of PD patients, the first treated with levodopa alone and the second treated initially with selegiline and then subsequently started on levodopa therapy on an as-needed basis. For a similar symptomatic effect, the sole difference after 3 to 5 years of treatment was that patients in the selegiline plus levodopa group received less levodopa than patients who received monotherapy.[72]

The DATATOP study[68] also investigated the effect of tocopherol (vitamin E), which traps free radicals, in patients with PD. The study failed to show any beneficial effect of tocopherol or any interaction between selegiline and tocopherol.[68]

3.2.2 Antioxidative Properties of Dopamine Agonists

Recent literature also discusses the putative neuroprotective actions of dopamine agonists.[39] Pergolide, like selegiline, elevates superoxide dismutase activity in the brain, decreases hydrogen peroxide formation from dopamine and preserves nigral cells in aging rats.[73-75] Bromocriptine, apomorphine and other agonists also scavenge free radicals and have antioxidant activity, in contrast with the mainly pro-oxidant actions of levodopa.[76] However, these studies are only *in vitro* experiments, and the clinical consequences of such properties remain to be determined.

3.2.3 Experimental Interventions Affecting Brain Iron

The demonstration that iron, which accumulates in the substantia nigra in patients with PD, can exert direct toxic effects on nigral neurons led to the search for new pharmacological approaches. These approaches are: (i) reducing the entry of iron into the brain; (ii) increasing the nontoxic storage of iron; (iii) removing (chelating) accumulated iron; and (iv) a combination of these interventions.[65] No clinical data using such therapeutic strategies have yet been published.

Table IV. Potential neuroprotective therapies for Parkinson's disease (from Jankovic,[69] with permission)

Strategy	Example
Levodopa-sparing strategies	Dopamine agonists
Dopamine receptor agonists	Bromocriptine Lisuride Pergolide
Dopamine transport inhibitors	Mazindol
Antioxidants	21-Aminosteroids MAO-A and MAO-B inhibitors
Lipid peroxidation inhibitors (free radical scavengers)	Tocopherol (vitamin E) Ascorbic acid (vitamin C) β-Carotene Lazaroids 21-Aminosteroids
Free radical trappers	Phenylbutylnitrone
Calcium antagonists	Dihydropyridines
Iron chelators	Desferoxamine (desferrioxamine) 21-Aminosteroids
Glutamate antagonists	NBQX Remacemide Amantadine Certain anticholinergic drugs Lamotrigine
Trophic factors	BDNF IGF FGF EGF GM1 gangliosides GDNF
Restorative therapy with brain implants	
Subthalamotomy	
Control of potential risk factors	

Abbreviations: BDNF = brain-derived neurotrophic factor; EGF = epidermal growth factor; FGF = fibroblast growth factor; GDNF = glial cell line-derived neurotrophic factor; IGF = insulin-like growth factor; MAO = monoamine oxidase; NBQX = 2,3-dihydroxy-6-nitro-7-sulfamoyl benzo(f)quinoxaline.

3.2.4 Other Strategies

Several other mechanisms have been reported to be involved in nigral cell death in patients with PD. These include a possible role for MPTP-like bioactivated neurotoxins and abnormalities in the enzymes regulating the metabolism of xenobiotic substances, particularly the hepatic cytochrome P450 system.[77,78] These observations led several investigators to propose that the evolution of the disease could be prevented via various methods, which were recently reviewed in *CNS Drugs*:[78] MAO inhibitors, dopamine transporter blockers, glutamate receptor antagonists, calcium antagonists, glutathione-type drugs and neurotrophic factors[78] (table IV).

Growth factors (e.g. basic fibroblast growth factor) have been shown to have potent effects on grafted dopamine neurons in rats with experimental PD.[79] This kind of study also suggests new approaches for enhancing the survival and function of dopamine neuron grafts. However, no clinical data are yet available.

Moreover, as discussed in section 3.2.1, new clinical methodologies for investigating a new drug with putative neuroprotective properties need to be developed.

3.3 Prevention and Early Diagnosis

The most important medical challenge in PD is to prevent the occurrence of the disease. The first area of this research is the study of drugs and toxins known to cause parkinsonism. In fact, of the secondary parkinsonisms, the most frequently observed clinical situation is drug-induced parkinsonism. It is often difficult to clinically differentiate idiopathic and drug-induced parkinsonism. Recent data indicate that, besides classical antipsychotics, parkinsonism can also be caused by calcium antagonists and some psychotropic and cardiotropic drugs.[80]

The drugs listed in table V must be avoided in patients with PD. Investigations into the mechanism of drug-induced parkinsonism could lead to new discoveries in the pathophysiology of the disease. For example, it has been shown that haloperidol and chlorpromazine inhibit complex I *in vitro* to rat brain mitochondria as well as in platelets.[30]

It would also be advantageous to be able to detect idiopathic PD before symptoms develop. Several techniques, such as radioimaging (positron emission tomography or single photon emission tomography), physiological and biochemical tests, are currently being studied but no definite conclusions can be reached at present.[81,82]

Table V. Summary of the main data concerning drug-induced parkinsonism (from Montastruc et al.[162] with permission)

Pharmacological class	Drugs	Intensity of the parkinsonian syndrome	Mechanism of action	Comments
Antiadrenergic drugs	Reserpine	+++	Depletes dopamine stores	
	Tetrabenazine	+++	Depletes dopamine stores	
Antipsychotics	Phenothiazines	++	Dopamine receptor blockade	
	Butyrophenones	+++	Dopamine receptor blockade	
	Thioxanthenes	++	Dopamine receptor blockade	
	Dibutylpiperidines	+++	Dopamine receptor blockade	
	Benzamides	+	Dopamine receptor blockade	Very rare with metopimazine and domperidone
	Clozapine	0 to +	Dopamine receptor blockade/antimuscarinic properties	
	Loxapine	++	Dopamine receptor blockade	
Antihypertensives	Methyldopa	0 to +	False neurotransmission	Rare
Calcium antagonists	Flunarizine	0 to +	Dopamine receptor blockade	Very rare with diltiazem or verapamil; dihydropyridines are also unlikely to cause this effect
	Cinnarizine	0 to +	Dopamine receptor blockade	
Antidepressants	Fluoxetine	0 to +	?	Not with imipramine derivatives
Antiarrhythmics	Amiodarone	0 to +	?	Yet to be confirmed

Symbols: 0 indicates absent; + indicates slight; ++ indicates marked; +++ indicates very marked; ? indicates that the mechanism of drug-induced parkinsonism remains to be determined.

4. Conclusions

New strategies for improving the treatment of PD are currently under development. These include drugs acting on the classical pharmacological target in PD (the nigrostriatal dopamine system): controlled-release preparations of levodopa, COMT inhibitors and new dopamine agonists, as well as new routes of administration of established dopaminergic drugs. A second goal is to find drugs that improve or correct symptoms resistant to levodopa therapy, such as freezing, falls and orthostatic hypotension. Thirdly, the major challenge remains to find a true neuroprotective drug in order to retard or prevent free radical damage.

Finally, the management of PD must aim to maintain an equilibrium between the satisfactory control of extrapyramidal symptoms and the long-term effects of levodopa administration. The 2 most exciting challenges in the future pharmacological approach to PD may lead to: (i) the development of effective antiparkinsonian drugs that do not exhibit the long-term adverse effects associated with levodopa (abnormal movements, fluctuations in performance, psychosis); and (ii) the introduction of true 'antidyskinetic' agents that do not aggravate extrapyramidal symptoms, as is the case with currently available antipsychotics.

These points underline the need for new, effective drugs and new clinical methodologies for drug evaluation, in addition to well-performed, long-term pharmacoepidemiological trials to test the numerous hypotheses raised by the growing field of basic neuroscience.

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